

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee : HESSEL, Lasse  
Patent No.: 4,976,273 (U.S.S.N. 07/148,992)  
Issue Date: December 11, 1990 (File Date: January 27, 1988)  
Assignee : Chartex International Plc  
Title : TUBULAR PROTECTIVE DEVICE FOR  
PROTECTION AGAINST TRANSFER OF  
INFECTIOUS MATTER DURING SEXUAL  
INTERCOURSE

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REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents and Trademarks  
Box Pat. Ext.  
Washington, D.C. 20231

Sir:

Pursuant to Section 201(a) of the Drug Price and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Chartex International Plc ("Chartex"), owner of the above-identified patent, hereby requests an extension of the patent term of U.S. Patent 4,976,273. Title to the invention and patent to Chartex are recorded by the following assignment documents:

- (1) From Dr. Lasse Hessel to International Trade House Ltd. which was recorded on October 21, 1987, at reel 4768 and frames 0896 and 0897;
- (2) From International Trade House Ltd. to Medicor Limited (Corporate name changed to Medicor International Limited on June 18, 1987) which was recorded on April 18, 1990, at reel 5278 and frame 0708 and 0708A;

- (3) From Medicor International Limited to Benchmark Investments Limited which was recorded on April 18, 1990, at reel 5278 and frame 0709; and
- (4) From Benchmark Investments Limited to Chartex International Plc which was recorded on April 18, 1990, at reel 5278 and frame 0710.

In accordance with 35 U.S.C. §156 (d) and 37 C.F.R. § 1.740, applicant Chartex submits the following information:

- (1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics, 37 C.F.R. § 1.740(a)(1).

The approved product is a medical device known by either the mark REALITY or the mark FEMIDOM. The device is a soft, loose-fitting plastic pouch that lines the vagina. It has a soft ring at each end. The ring at the closed end is used to put the device inside the vagina and holds it in place. The other ring stays outside the vagina and partly covers the lip area.

Specifically, the REALITY or FEMIDOM product is:

- (a) a flexible, thin-walled tube having a sufficiently large first diameter to permit movement of a penis within the tube during coitus, the flexible thin-walled tube has a closed end and an open end, the open end has:
  - (i) a collar-shaped, outwardly extending portion;
  - and

- (ii) a first elastic ring integrally connected with the collar-shaped portion having a second diameter larger than the first diameter;
- (b) a means for retaining located in the closed end of the flexible, thin-walled tube and having a diameter sufficient to maintain the means for retaining in a vagina of an user.

Approved labeling and instructions for use of the REALITY or FEMIDOM product are annexed as Appendix A. The items in Appendix A form a complete description of the REALITY or FEMIDOM female condom.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred, 37 C.F.R. § 1.740(a)(2).

The regulatory review occurred under Section 515 of the Federal Food, Drug and Cosmetic Act ("FFDCA").

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred, 37 C.F.R. § 1.740(a)(3).

The REALITY female condom was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to Section 515 of the FFDCA on May 7, 1993. See, Appendix B.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or with active ingredients), the use for which it was approved, and the provision of law under which it was approved, 37 C.F.R.

§ 1.740(a)(4).

The product is not a drug. Therefore, this section is not applicable.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted, 37 C.F.R.

§ 1.740(a)(5).

The REALITY and FEMIDOM female condom was approved on May 7, 1993, and the last day of the sixty day period permitted for the extension of a patent is July 6, 1993. The application was hand delivered to the Assistant Commissioner of Patents and Trademarks on July 2, 1993, and is, therefore, timely filed within the sixty day limit.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration, 37 C.F.R. § 1.740(a)(6).

Inventor: Lasse Hessel  
U.S. Patent No. 4,976,273  
Issued: December 11, 1990  
Expiration Date: April 5, 2005

(7) A copy of the patent for which the extension is being sought, including the entire specification (including claims) and drawings, 37 C.F.R. § 1.740(a)(7).

A copy of U.S. Patent No. 4,976,273 is attached as Appendix C.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent, 37 C.F.R. § 1.740(a)(8).

Copies of the terminal disclaimer, and the request for a certificate of correction for U.S. Patent No. 4,976,273 are attached as Appendix D.

U.S. Patent No. 4,976,273 is based upon a continuation application of prior U.S. patent application 07/058,766 which was filed on June 5, 1987, and which issued as U.S. Patent No. 4,735,621 on April 5, 1988.

This request for extension of patent term is filed concurrently with a request for extension of patent term for U.S. Patent No. 4,735,621. Upon receipt of an indication of

allowability for the two requests, Chartex will submit an election of one of the two requests and will withdraw the other request for extension of patent term.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product, 37 C.F.R. § 1.740(a)(9).

Claims 1, 2, and 4 read on the REALITY or FEMIDOM female condom as follows:

The REALITY or FEMIDOM female condom is a tubular protective device for protection against a transfer of infectious matter during sexual intercourse. The condom comprises a flexible, thin-walled tube that is closed at one end and has an open end, a collar-shaped, outwardly extending portion at the open end as described in claims 1, 2, and 4. The inner diameter of the device is sufficiently large to permit movement of a penis with respect to the tubing of the device during coitus or sexual intercourse as per claims 1, 2, and 4. Further, as set forth in claims 1, 2, and 4, the REALITY or FEMIDOM female condom has a "means for retaining" located in the closed end and having a diameter sufficient to maintain the device in the user's vagina.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review as follows:

. . . .

(v) For a patent claiming a medical device, the effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device if no IDE was submitted and any available substantiation of that date; the date on which the application for product approval or notice of completion of product development protocol under section 515 of the Federal Food, Drug, and Cosmetic Act was initially submitted and the number of the application or protocol; and the date on which the application was approved or the protocol declared to be completed.

. . . .

37 C.F.R. § 1.740(a)(10)(v).

<u>IDE PURPOSE*</u>	<u>IDE NUMBER</u>	<u>DATE</u>
Reinfection Rate	G900114	July 6, 1990
Vaginal Trauma	G890229	June 25, 1989
Use Effectiveness	G890203	March 8, 1990
Instructions for Use	G900001	February 1, 1990
Anal Intercourse	G900066	September 18, 1990
Rip-Tear Study	G920064	April 10, 1992

\* See, Appendices G and I.

The application for product approval for the REALITY or FEMIDOM female condom under section 515 of the FFDCA was submitted on October 29, 1991, as PMA Number P910064.

The FDA approved P910064 on May 7, 1993. See, Appendix B.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities, 37 C.F.R. § 1.740(a)(11).

During the applicable regulatory review period, Chartex, through the activities of its licensee, Wisconsin Pharmacal Company Inc. ("Wisconsin Pharmacal"), was actively involved in obtaining premarket approval for the REALITY or FEMIDOM female condom. Wisconsin Pharmacal initiated clinical research and development of the female condom in the United States in April 1988. On October 29, 1991, Wisconsin Pharmacal filed PMA Number P910064 with the FDA. The time line set forth in Appendix E details the significant activities undertaken with respect to the approved product during the applicable regulatory review period. In addition, Appendices F and G, respectively, provide the Clinical Trial and Survey Summary Report and the Summary of Clinical Studies Worldwide using the REALITY or FEMIDOM product. These tests and evaluations were undertaken in the United States by Wisconsin Pharmacal and on a worldwide basis by applicant, Chartex. See, Appendices H and I.

The applicant notes that the regulatory period included 27 amendments of the PMA prior to issuance of the letter designating the female condom as "approvable" on April 26, 1993. Two

additional amendments were submitted between April 26, 1993, and the final approval for commercial marketing by the FDA on May 7, 1993. Wisconsin Pharmacal authorized Chartex to rely upon the regulatory review period for the REALITY or FEMIDOM female condom on April 15, 1993. See, Appendix K.

(12) Statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of the extension was determined, 37 C.F.R.

§ 1.740(a)(12).

(a) Chartex believes that the patent is eligible for extension under 35 U.S.C. § 156 (a) as follows:

Section 156(a) provides in pertinent part, that the term of a patent which claims a product shall be extended if: (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent never has been extended, (3) an application for extension is submitted in accordance with 35 U.S.C. §156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

In the present case, each of these elements is satisfied as indicated below:

(1) The term of U.S. Patent No. 4,976,273 expires on April 5, 2005. Therefore, this application has been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by Chartex International Plc, the owner of the patent. This application is submitted in accordance with 35 U.S.C. §156(d), in that it is submitted within the sixty-day period beginning May 7, 1993, the date the product received permission for marketing from the FDA. See, Appendix B. Further, the present application complies with the requirements of an application under 35 U.S.C. §156(d) and the applicable sections of the C.F.R., including 37 C.F.R. § 1.740.

(4) As evidenced by the May 7, 1993, letter from the FDA, the product was approved in accordance with Section 515 of the Federal Food, Drug, and Cosmetic Act.

(5) Finally, and in accordance with 35 U.S.C. §156(a)(5)(A), Chartex asserts that the permission for the commercial marketing or use of the REALITY or FEMIDOM female condom is the first permitted marketing or use of that product under the provision of law under which such regulatory review period occurred.

(b) Statement as to the length of extension claimed.

The term of U.S. Patent No. 4,976,273 should be extended 717 days to March 24, 2006. This extension was determined on the following basis:

The calculation of a patent term extension for a medical device is set forth in 37 C.F.R. § 1.777. The rule first requires that the length of the regulatory review period be

determined. This period is the sum of the number of days in the period beginning on the date a clinical investigation on humans involving the device was begun and ending on the date on which an application under Section 515 of the FDCA was initially submitted, and the number of days in the period beginning on the date the application was initially submitted with respect to the device and ending on the date such application was approved, 37 C.F.R. §1.777(c)(1-2).

In the present case, clinical evaluations of the REALITY or FEMIDOM female condom on humans were in progress in 1987 prior to the issue date of the patent for which extension is sought. See, Appendix J. The applicant is claiming April 6, 1988, as the date of initial human testing. An application for approval was submitted on October 29, 1991 (PMA Number P910064). Accordingly, the total number of days for this period is 1301.

The number of days between the application date and final approval on May 7, 1993, is 556. Therefore, the length of the regulatory period prior to any necessary subtractions is 1857 days.

The term for which a patent may be extended is set forth at 37 C.F.R. §1.777(d). Under subsection (d)(1) of that rule, there may be certain subtractions from the regulatory review period as determined above. These potential subtractions are as follows:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on or before the patent issued;

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that the applicant did not act with due diligence;

(iii) One-half the number of days determined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(1) and (ii) of this section; half days will be ignored for purposes of subtraction....

In this instance, no subtractions under (d)(1)(ii) are applicable since the applicant acted with due diligence. Under (d)(1)(i), there were 979 days between the date of initial human clinical testing and the issue date of U.S. Patent 4,976,273 on December 11, 1990. Therefore, the number of days in paragraphs (c)(1) and (c)(2) must be reduced by 979 days yielding a period of 878 days.

Under subparagraph (iii), reduction of the 1301-day period determined by paragraph (c)(1) less 979 days, by one-half yields 161 days. Therefore, after all appropriate subtractions and reductions, the regulatory period is 717 days. Expressed as a

formula, this figure is obtained by calculating  $1301 - 979(0.5 \times 332) + 556$  or  $(c)(1) - (d)(1)(i)[0.5 \times (c)(1) - (d)(1)(i)] + (c)(2)$  where the variables correspond to the subparagraphs of the rule.

Next, 37 C.F.R. §1.777(d)(2)-(5) require that certain dates be calculated and compared. Under (d)(2) adding 717 days to April 5, 2005, the original term of the patent (there being a terminal disclaimer to this date), yields a date of March 24, 2006. Under subparagraph (d)(3), adding 14 years to the date of approval of the application under section 515 of the FDCA (14 years from May 7, 1993) provides a date of May 7, 2007. As required by (d)(4), comparing the two periods obtained under (d)(2) and (3), respectively, yields an earlier date of March 24, 2006. Because the patent issued after September 24, 1984, subparagraph (d)(5) requires that five years be added to the original expiration date of the patent (April 5, 2005) and the result compared with the result obtained pursuant to subparagraph (d)(4). Adding five years to the patent's expiration date presents a date of April 5, 2010. This date is later than that computed under (d)(4) which is March 24, 2006.

Accordingly, the patent term should be extended by 717 days to March 24, 2006, this being the number of days between the normal expiration of the patent on April 5, 2005 and the earliest date determined under (d)(4).

(13) A statement that the applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought, 37 C.F.R. § 1.740(a)(12).

Chartex acknowledges its duty of disclosure and is unaware of any further information, which is material to the determination of entitlement, other than that information already presented in this application, including the attached exhibits.

(14) The prescribed fee for receiving and acting upon the application for extension, 37 C.F.R. § 1.740(a)(14).

Applicant is submitting the prescribed fee for receiving and acting upon the application in the amount of \$1,000. The Office is authorized to charge any underpayment or to credit any overpayment to our Deposit Account No. 12-1210.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed as follows, 37 C.F.R. § 1.740(a)(15).

The Office is requested to direct all inquiries and correspondence relating to this application for patent term extension to

Paul Grandinetti  
Levy, Zito & Grandinetti  
Suite 411  
1910 K Street, N.W.  
Washington, D.C. 20006-1104  
Telephone (202) 429-4560  
Facsimile (202) 429-4564.

(16) A duplicate of the application papers, certified as such, 37 C.F.R. § 1.740(a)(16).

Chartex is submitting herewith a duplicate copy of this application, certified as such.

(17) An oath or declaration as set forth in paragraph (b) of this section, 37 C.F.R. § 1.740(a)(17).

The undersigned declares as follows:

(a) He is a registered patent attorney authorized to practice before the U.S. Patent and Trademark Office and has general authority from Chartex International Plc, the owner of record of U.S. Patent No. 4,976,273, to act on its behalf in patent matters;

(b) He has reviewed and understands the contents of the application being submitted concurrently herewith, namely, an application for the extension of U.S. Patent No. 4,976,273;

(c) He believes that the patent is subject to the extension sought pursuant to 37 C.F.R. § 1.710;


(d) He believes that an extension of the length of time claimed is justified under 35 U.S.C. § 156 and the applicable regulations;

(e) He believes that the patent for which the extension is sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720; and

(f) He believes that all statements made herein of his own knowledge are true and that all statements made upon information and belief are believed to be true and that the statements were made with the knowledge that willful false statements and the like are punishable by fine imprisonment, or both under Title 18, Section 1001 of the United States Code, and that such willful false statements may jeopardize this application.

Respectfully submitted,

1 July 1993  
Date

  
Paul Grandinetti  
Reg. No. 30,754

LEVY, ZITO & GRANDINETTI  
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## Appendices

Appendix A-Approved labeling and for the use of the REALITY/FEMIDOM female condom.

Appendix B-Approval by the FDA for commercial marketing of the REALITY/FEMIDOM female condom.

Appendix C-Copy of U.S. Patent No. 4,976,273.

Appendix D-Copy of the request for a certificate of correction and a copy of the Terminal Disclaimer for U.S. Patent No. 4,976,273.

Appendix E-Time line detailing the significant activities undertaken with respect to the approved product during the applicable regulatory review period.

Appendix F-Clinical Trial and Survey Summary Report.

Appendix G-Summary of Clinical Studies Worldwide.

Appendix H-Letters regarding the PMA and Amendments to PMA and FDA correspondence regarding same.

Appendix I-Correspondence regarding IDEs.

Appendix J-Article Re: Commencement of Human Clinical Testing.

Appendix K-Authorization to Rely on Regulatory Review Period.

REVISED LABELING FOR REALITY™ THE FEMALE CONDOM

The following statement will appear prominently on the carton and device package. It will also appear prominently (highlighted or in a box) as the first statement on the instructions for use.

"KEY ELEMENT"

Important Information:

- Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly.
- If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.
- Reality only works when you use it. Use it every time you have sex.
- Before you try Reality, be sure to read the directions in the box and learn how to use it properly.

A. Package Insert/Instruction Leaflet\*

Important Information:

- Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly.
- If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.
- Reality only works when you use it. Use it every time you have sex.
- Before you try Reality, be sure to read the directions in the box and learn how to use it properly.

REALITY™ Female Condom

Reality is intended to be worn by women during sex. It can help prevent pregnancy and sexually transmitted diseases, including AIDS (HIV infection).

Because Reality is new, it may look different to you or you may feel nervous about trying to insert it -- similar perhaps to how you felt the first time you inserted a tampon, or a diaphragm. After you become used to Reality, it should become easier and more comfortable to use.

It's important to practice putting Reality in without having sex. Take your time. Get familiar with Reality's different shape and the way it looks. See how it hangs outside the vagina when in place.

1. Product Overview

a. Description

Reality is a soft, loose-fitting plastic pouch that lines the vagina. It has a soft ring at each end. The ring at the closed end is used to put the device inside the vagina and holds it in place. The other ring stays outside the vagina and partly covers the lip area.

Use a new Reality with each sex act. If you use it again, do not expect it to protect you. Use a new Reality every time you have sex.

b. Precautions

Here are some important things to remember in order to get the best protection from Reality:

- (1) Use Reality every time you have sex. If Reality is not used every time, your risk of becoming pregnant or getting a sexually transmitted disease will be higher.
- (2) Use a new Reality with each sex act. If you use it again, do not expect it to protect you.
- (3) Do not remove Reality's inner ring. This ring helps keep the device in place during use. If you remove the ring, Reality will not work as well.
- (4) Do not use Reality and a male condom at the same time. If you do, both products will not stay in place.
- (5) Don't tear Reality. Be careful of sharp objects, like rings or jagged fingernails. If Reality should tear, remove it and use a new one.
- (6) Use more lubricant if needed. If the device comes out of the vagina during use, or if the outer ring gets pushed inside, use a new Reality. Also, add some extra lubricant. You can put the lubricant either inside the device or on the man's penis. The added lubricant may also make Reality more comfortable to use and may allow the penis to slip easily in and out of the vagina.

c. About Reality's Effectiveness

How Reality was tested

Limited laboratory tests showed that Reality can block the germs that cause sexually transmitted diseases. Reality was only tested in humans for its ability to prevent pregnancy. That's because researchers did not want to take a chance on exposing people in the tests to AIDS and other sexually transmitted diseases. The idea was that if Reality can prevent sperm from entering the woman and causing pregnancy, it can also prevent spreading the germs that cause sexually transmitted diseases.

Reality was tested for use over 6 months in U.S. women. This was not as long and did not include as many women as other contraceptive studies. The study shows Reality provides protection against pregnancy. The pregnancy rate in the 6-month study was 13%. The estimated 1 year pregnancy rate for Reality ranges from 21% to 26%. This means that about one in four women who use Reality may become pregnant during a year. Couples who used Reality correctly with every sex act had a lower pregnancy rate.

This table shows the overall pregnancy rates from studies of barrier contraceptives. Depending on if you use the method correctly every time you have sex, your risk of pregnancy may be higher or lower. Other contraceptive products not listed here, such as birth control pills, are more effective at preventing pregnancy.

"KEY ELEMENT"

Overall Pregnancy Rates for Barrier Contraceptives

Condoms Which Protect Against Pregnancy and Sexually Transmitted Diseases

	<u>Pregnancy Rates**</u>	
	<u>6 Months</u>	<u>1 Year</u>
Reality Female Condom*	13%	26%
Male Latex Condom <sup>1</sup>	8%	15%

Pregnancy Rates with Other Methods

	<u>Pregnancy Rates**</u>	
	<u>6 Months</u>	<u>1 Year</u>
Cervical Cap	10%	18%
Diaphragm	8%	15%
Sponge	12%	17%

	<u>Pregnancy Rates</u>
	<u>1 Year</u>
Unprotected sex <sup>2</sup>	85%

\* Yearly failure rates for Reality were estimated by doubling the 6-month pregnancy rate.

\*\* Pregnancy rates for Reality, Cervical Cap, Diaphragm and Sponge are from clinical trials. Actual use failure rates may be higher or lower.

<sup>1</sup> 1988 National Survey of Family Growth.

<sup>2</sup> Trussell, et.al., Studies in Family Planning 21(1), Jan/Feb 1990.

Remember - Reality can only work if you use it. Also remember - if you are trying to prevent sexually transmitted diseases - there is no "safe" time when you can have sex without protection. Use Reality every time you have sex.

If you must not become pregnant because of a medical condition, talk to your doctor or family planning clinic before using any contraceptive.

d. When to Use Reality

Reality can be inserted up to 8 hours before sex. However, most women insert Reality between 2 to 20 minutes before sex.

Reality should be removed after sex and before you stand up. It is for one-time use. Use a new Reality with each sex act.

2. Problems using Reality - Some women have reported problems using Reality. One of the problems is the outer ring can be pushed inside the vagina during sex. Some women have also reported that the penis slipped to the side of the device on entering the vagina. Other problems included difficulty inserting Reality, minor irritation, discomfort and breakage.

3. Storage Instructions

Store Reality at normal room temperature. Do not use Reality after its expiration date because it will not work as well.

SOME FEATURES OF USING REALITY

- You can insert Reality yourself. It gives you a way to protect yourself.
- Reality warms up as soon as you insert it. It is both strong and soft.

## INSTRUCTIONS FOR USE

### To Open the Packet

- Pull the two sides of the packet apart from the center of the top.
- Take out Reality and look at it closely.
- Rub the outside of the pouch together to be sure the lubrication is evenly spread inside.
- To add more lubricant, simply give one quick squeeze of the extra lubricant. Try different amounts to see what's best for you and your partner. Try starting with 2 drops.

### To Insert Reality

- Find a comfortable position. Try standing with one foot up on a chair, or sit with knees apart, or lie down.
- Be sure the inner ring is at the bottom, closed-end of the pouch.
- If you wish, add a drop of extra lubricant to the closed-end outside tip of the pouch or to the outside ring before you insert Reality.
- Hold the pouch with the open end hanging down. While holding the outside of the pouch, squeeze the inner ring with your thumb and middle finger.
- Place your index finger between the thumb and middle finger and keep squeezing the inner ring. FIG. C.

- Still squeezing Reality with your three fingers, with your other hand, spread the lips of your vagina and
- Insert the squeezed Reality as shown in FIG. D.

Take your time. If Reality is slippery to insert, let it go and start over.

- Now push the inner ring and the pouch the rest of the way up into the vagina with your index finger. CHECK TO BE SURE THE INNER RING IS UP JUST PAST THE PUBIC BONE. Look at FIG. E. You will feel the pubic bone by curving your index finger when it is a couple of inches inside the vagina. (Please label the pubic bone on the diagram.)

This step may be hard to do on the first or second try because Reality is lubricated.

Take your time and push Reality up to where you can feel the bone.

Make sure Reality is inserted straight (not twisted) into the vagina. It is also important that the OUTSIDE RING LIES AGAINST THE OUTER LIPS AS SHOWN IN FIG. F.

About one inch of the open end will stay outside your body. See FIG. F. While this may look unusual, this part of Reality helps protect you and your partner during sex. Once the penis enters, the vagina will expand and the slack will decrease.

Until you and your partner become comfortable using Reality, use your hand to guide the penis into the pouch. See FIG G.

After two or three times, you should become familiar with

using Reality and should hardly notice the sheath or the outer ring during sex. For added comfort, you may want to add more lubricant either inside or outside Reality. Some couples like to add extra lubricant directly to the penis.

#### During Intercourse

You may notice that Reality moves around during sex. See FIG. H.

- Movement side-to-side of the outer ring is normal.
- Sometimes Reality may slip up and down in the vagina, "riding" the penis. If you notice Reality is slipping, add lubricant to the penis or inside the pouch.
- If you begin to feel the outer ring being pushed into the vagina, STOP. See figure x. If the penis starts to enter underneath or beside the sheath, STOP. See figure y. Take out Reality. Put it in a new Reality, and add extra lubricant to the opening of the pouch or on the penis. Make sure the outside part lies over the lip area.

### After Intercourse

To take out Reality, squeeze and twist the outer ring to keep the sperm inside the pouch. Pull out gently. Throw away in a trash can. Do not flush. Do not reuse. FIG. I.

### Remember

To help reduce your risk of pregnancy and spreading or getting a sexually transmitted disease:

- Use a new Reality every time you have sex.
- Follow the directions carefully.
- Be sure you don't tear the sheath with fingernails or other sharp objects.
- Use enough lubricant.

## Questions You May Have About the Proper Use of Reality

### 1. WILL REALITY ALWAYS PROTECT AGAINST PREGNANCY AND STDs?

No method is 100 percent effective. Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly. If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.

### 2. HOW DO I KNOW WHEN REALITY IS UP FAR ENOUGH?

Using your index finger, push the device so that the lower ring of the device is against the pubic bone. You will find the pubic bone by curving your index finger when it is a couple of inches inside the vagina.

### 3. WHAT DO I DO IF THE OUTER RING IS PUSHED INSIDE THE VAGINA?

STOP. Remove the Reality device. Insert a new Reality according to the directions. Add extra lubricant to inside the device at the opening of the vagina. Consider lubricating the penis also. This problem can occur if there isn't enough lubricant, or if the inner ring isn't in the proper position.

### 4. WILL REALITY BE NOISY DURING SEX?

If properly lubricated, there should be little noise. If you experience noise during sex, add extra lubricant.

### 5. WHAT IS THE PURPOSE OF THE LUBRICANT?

The lubricant helps the penis move freely in and out, prevents

slipping, and discomfort. If the penis does not slip in and out easily, add more lubricant.

6. WILL I FEEL REALITY ONCE IT IS IN PLACE?

Some people may feel Reality and some may not if it is properly in place and lubricated.

7. WHAT DO I DO IF THE PENIS IS INSERTED OUTSIDE THE POUCH?

STOP. Remove the penis. Insert a new Reality and make sure the outer ring lies flat over the lip area. When you reinsert the penis, guide it with your hands. Do not let the penis directly touch the vagina.

8. WILL REALITY RIP OR TEAR WHILE I AM USING IT?

Studies show that Reality rips or tears less than 1% of the time. If you think Reality has been ripped or torn, remove it right away, throw it away, and insert a new Reality.

9. WILL REALITY BUNCH UP INSIDE THE VAGINA?

Reality should not bunch up inside if it is inserted right and if there is enough lubricant. If you feel the outer ring begin to slip inside, STOP. Remove the Reality device. Insert a new Reality device according to the directions. Add extra lubricant inside the device at the opening of the vagina.

12. WHAT DOES THE OUTER RING FEEL LIKE DURING SEX?

While aware that the outer ring is there, most women say that once they become comfortable with how it looks, they forget about it and don't feel it during sex.

13. WHAT DO I DO IF REALITY DOES NOT STAY IN PLACE DURING SEX?

If Reality moves down the vagina causing discomfort, either push it back up or remove Reality. If you push it back up, add lubricant. If you remove Reality, use a new one and add extra lubricant.

- Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly.
- If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.

DO YOU HAVE A QUESTION ON  
HOW TO USE REALITY?  
CALL your doctor or family planning clinic  
or  
CALL 1-800-XXX-XXXX

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development  
Wisconsin Pharmacal Company, Inc.  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

MAY 7 1993

Re: P910064  
Reality™ Female Condom  
Filed: October 29, 1991  
Amended: December 17, 19, and 30, 1991; January 9, 15, and 31,  
February 26, April 13 and 15, June 24, July 16 and 31,  
August 3, September 28, October 30, November 16, December 1, 4,  
7, 16, and 18, 1992; January 22 and 29, February 2 and 9,  
March 3, April 15 and 28, and May 6, 1993

Dear Dr. Leeper:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Reality™ Female Condom. This device is indicated for use to help prevent pregnancy and sexually transmitted diseases, including the human immunodeficiency virus infection (HIV), during vaginal intercourse. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). At the April 22, 1993, meeting between CDRH and Wisconsin Pharmacal, you agreed to the specific conditions listed below with the exception of two specific points on the device labeling. These points were the pregnancy rates at 6 and at 12 months for your product (13% and 26%, respectively) listed on page six of the draft labeling. We note your amendment dated April 26, 1993, including an analysis by James Trussell, your expert on pregnancy failure rates. In view of this amendment, we have revised the table of the draft labeling. These revisions are shown on the following page. The column for the 1-year pregnancy rates must be more prominently high lighted than as shown (e.g., use of borders, shadowing, etc.).

In addition, we have added the following text to the device labeling:

"The pregnancy rate in the 6-month study was 13%. The estimated 1 year pregnancy rate for Reality ranges from 21% to 26%. This means that about one in four women who use Reality may become pregnant during a year."

As part of the heading to the above table just before the sentence "Your risk of pregnancy may be higher or lower...", we have added the phrase "depending on if you use the method correctly every time you have sex....".

We are enclosing these editorial changes and corrections to you as the final draft labeling (copy enclosed).

OVERALL PREGNANCY RATES FOR BARRIER CONTRACEPTIVES

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Condoms Which Protect Against Pregnancy and Sexually Transmitted Diseases

Pregnancy Rates\*\*

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	<u>6-Months</u>	<u>1 Year</u>
Reality™ Female Condom*	13%	26%
Male Latex Condom <sup>1</sup>	8%	15%

Pregnancy Rates for Other Methods

Pregnancy Rates\*\*

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	<u>6-Months</u>	<u>1 Year</u>
Cervical Cap	10%	18%
Diaphragm	8%	15%
Sponge	12%	17%

Pregnancy Rates

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	<u>1 Year</u>
Unprotected Sex <sup>2</sup>	85%

\* Yearly failure rates for Reality™ Female Condom were estimated by doubling the 6-month pregnancy rate.

\*\* Pregnancy rates for Reality™ Female Condom, Cervical Cap, and Sponge are from clinical trials. Actual use failure rates may be higher or lower.

<sup>1</sup> 1988 National Survey of Family Growth

<sup>2</sup> Trussell, et.al., Studies in Family Planning 21 (1), Jan/Feb 1990.

The agreed upon conditions of approval were conveyed to you in CDRH's approvable letter dated April 26, 1993. Your May 6, 1993, amendment provided written concurrence with the conditions of approval, and you may begin commercial distribution of the device upon receipt of this letter. Please note that you are required to incorporate these editorial changes and corrections exactly as directed in the device labeling, and to submit to FDA a copy of final patient labeling prior to marketing.

#### Specific Conditions

##### 1. Preclinical Requirements

- a. Initiate real-time aging studies to demonstrate the chemical and physical stability of the device materials (polyurethane and lubricant) to establish a shelf-life. (Devices from at least three production lots should be used to establish the shelf-life.) Until additional data are available, you may only label your device with a 18-month shelf-life.
- b. Provide data from *in vitro* permeability studies, such as the  $\phi$ X174 Bacteriophage Studies, to confirm the barrier properties of your device with respect to sexually transmitted diseases. (Devices from at least three production lots should be tested.)

##### Device Labeling and Promotion

- a. Revise the patient labeling according to the enclosure, and conduct focus group studies to refine the device labeling.
- b. Include the "key elements" identified in the labeling in all advertisements and promotions as discussed during the meeting.
- c. Provide within 45 days of the date of this letter professional labeling for the Reality™ Female Condom. This professional labeling should include indications for use, contraindications, warnings, precautions, adverse effects, and instructions for use (see enclosure).

##### 3. Future Clinical Requirements

Participate in future government sponsored studies of the Reality™ Female Condom. The details of the future participation will be negotiated as the plans progress.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

You should be advised that, pursuant to section 515(e)(3) of the Safe Medical Amendments Act of 1990, the Secretary may temporarily suspend approval and initiate withdrawal of this PMA if the Secretary finds that the device is unsafe or ineffective, or on the basis of new information with respect to the device, which when evaluated together with information available at the time of approval, indicates a lack of showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Colin Pollard at (301) 427-1180 or Melpomeni Jeffries at (301) 427-1186.

Sincerely yours,



David L. West, Ph.D.  
Deputy Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosures

## SUMMARY OF SAFETY AND EFFECTIVENESS

### I. General Information

Generic Name: Female Condom

Trade Name: Reality™ Female Condom

Applicant's Name: Wisconsin Pharmacal Company, Inc.  
2977 Highway 60  
Jackson, Wisconsin 53037

Premarket Approval Application (PMA) Number: P910064

Dates of Panel Recommendations: January 31, 1992  
December 10, 1992

Date of Notice of Approval to Applicant: MAY 7 1993

### II. Indications for Use

The Reality™ Female Condom (hereafter referred to as Reality™) is an intravaginal barrier device, especially for women whose sex partners do not use latex condoms. It is indicated for use to help prevent pregnancy and sexually transmitted diseases (STDs), including the human immunodeficiency virus (HIV) infection, during vaginal intercourse.

### III. Device Description

Reality™ is a loose-fitting polyether polyurethane sheath with two flexible polyether polyurethane rings. One ring lies inside at the closed end of the sheath, and serves as an insertion mechanism and as an anchor during use. The other ring forms the external edge of the sheath and remains outside the vagina after insertion. Once inserted, Reality™ lines the inner contours of the vagina. Reality™ is prelubricated with silicone. An additional water-based lubricant is individually packaged and supplied with each device. Reality™ is for single use only.

### IV. Contraindications, Warnings and Precautions

Use of Reality™ is contraindicated in the presence of any of the following conditions: (1) sensitization to the device materials or lubricant and (2) any active vaginal, vulvar or cervical infection.

The device should not be used by women who are unable to insert or remove device or follow the instructions for use. See the attached labeling for additional warnings and precautions (Attachment 1).

### V. Potential Adverse Effects of the Device on Health

Studies have shown that health risks associated with the use of the Reality™ include discomfort, vaginal irritation, penile irritation, sensitization to

device materials, urinary tract infection, vaginal and cervical infections, sexually transmitted diseases and unintended pregnancy.

## VI. Alternative Practices and Procedures

The latex male condom is the only commercially available product for reducing the risk of pregnancy and STDs, including HIV infection. There are, however, other available methods of contraception. Contraceptive barrier methods include the cervical cap, the diaphragm, the sponge and the condom. Nonbarrier methods of contraception include hormonal methods and intrauterine devices.

## VII. Marketing History

Reality™ is manufactured and distributed in Europe by Chartex International under the trademark Femidom. Femidom has the same product specifications as Reality™. Femidom became commercially available as an over-the-counter device between February 1992 and March 1993 in Switzerland, United Kingdom, Austria, The Netherlands, Portugal and Norway.

## VIII. Summary of Studies

### A. Nonclinical Laboratory Studies

#### 1. Physical and Chemical Properties

The applicant conducted tests to characterize the physical properties of the device. The test methodology for tensile strength and ultimate elongation was the American Society for Testing and Materials (ASTM) D-412. The instrument used to measure these parameters was an Instron Tester. The test methodology for burst pressure and volume was adopted from International Standards Organization (ISO) 4074/6. The test apparatus was a modification of a burst tester used for latex condoms.

The applicant established minimum tensile and burst strengths for the device. The device's minimal cross-grain and with-grain tensile strength at break was established at greater than 35 MPa. The minimal seam tensile strength at break was established at greater than 10.3 MPa. The minimal burst strength was established at 0.7 psi. These physical properties are considered adequate for the intended use of the device.

The device materials, polyether polyurethane, may contain the residual monomer methylene dianiline (MDA), a known animal carcinogen.<sup>1</sup> Samples of silicone-lubricated and non-lubricated Reality™ devices were extracted in 60 ml of distilled water at 37°C for 24 hours. The extracts were analyzed by reverse-phase liquid chromatography. MDA was not detected in any sample extract. The detection limits of the test were 5 parts per billion.

## 2. Biocompatibility:

A series of *in vitro* and *in vivo* biocompatibility tests were conducted on Reality™ and its additional lubricant to evaluate any potential acute and chronic toxicity, and to demonstrate the safety of the device materials for their intended use.

### a. In-Vitro Toxicity

1. Cytotoxicity: A non-lubricated Reality™ device was tested according to U.S. Pharmacopeia procedures for cytotoxicity in mouse L-929 cells.<sup>2</sup> There were no differences in the cytopathic index and cytotoxic index between the device extract and the negative control.
2. Mutagenicity: Non-lubricated Reality™ devices were extracted in saline (0.9%) and ethanol (100%) at 50°C for approximately 76 hours. Extracts were tested in the Ames *Salmonella typhimurium* Test. Neither extract increased the number of his- to his+ *S. typhimurium* revertants in the assay.

### b. Acute Toxicity

1. Primary Dermal Irritation: Non-lubricated Reality™ devices were applied to one intact and one abraded site on the back of six New Zealand rabbits for 24 hours. Testing sites were evaluated for erythema and edema using the Draize criteria. There were no differences in erythema and edema between abraded and intact tissue surfaces at 24 and 72 hours.
2. Dermal Sensitization: The silicone lubricated Reality™ device plus additional water-based lubricant, the additional water-based lubricant alone, and saline (0.9%) and cottonseed oil (100%) extracts of the Reality™ devices were tested using a modified Buehler procedure with 10 albino guinea pigs per group.<sup>3</sup> Testing sites were evaluated for erythema and edema using the Draize criteria approximately 24 and 48 hours after the challenge application. No signs of erythema or edema were observed at the challenge sites.
3. Acute Vaginal Mucosal Irritation: Silicone lubricated Reality™ devices (60cm<sup>2</sup>) were minced, and combined with 10ml of additional water-based lubricant and 10ml of K-Y Jelly. 0.5ml of each test sample was administered into the vaginal vault of 10 white New Zealand rabbits for 5 days. Another group of 10 rabbits was administered either 0.5ml of the additional water-based lubricant or K-Y Jelly for 5 days. The K-Y Jelly was used as a control. Histopathological examinations on all animals were performed and scored by scalar notation. There were no significant differences in the scores between the control and treatment groups. Both were considered mild irritants.

4. Acute Systemic Toxicity: Device extracts were tested according to U.S. Pharmacopeia procedures using five mice per device extract. Silicone lubricated Reality™ devices with and without the additional water-based lubricant were extracted in saline (0.9%), ethanol in saline (5%), cottonseed oil and polyethylene glycol. There were no systemic toxic effects in mice from the administration of any of the extracts.

c. Chronic Toxicity

1. Chronic Vaginal Irritation: Ten white New Zealand rabbits (group 1) received between 20 to 24 treatments of glass beads coated with the silicone lubricated Reality™ device. Ten animals (group 2) received between 20-26 treatments of glass beads which were not coated with the silicone lubricated Reality™ device. Another control group (group 3) received no treatment. The beads, which were secured to a 26cm silk suture, were introduced into the vagina and remained in place for 4 hours.

Histopathologic examinations were conducted on three sections of each vagina and scored by scalar notation. The mean total histological score for the Reality™ coated glass beads was slightly higher than the mean score for the glass beads alone, indicating that the Reality™ coated glass bead caused slight vaginal mucosal irritation.

Silicone lubricated Reality™ devices were extracted with saline (0.9%) and cottonseed oil (100%) according to U.S. Pharmacopeia procedures. Extracts were tested as described above except that a 0.5 ml sample was administered into the vaginal vault. There were no significant differences in mean total histopathological scores between the device extracts and extracts alone.

3. Barrier Transport Studies

a. Methodology

Virus penetration tests were performed in a two chamber, dynamic pressure apparatus. The device was prevented from expanding under pressure by an open-mesh restrainer. The dynamic test included pulsed pressure, with a periodic (30 cpm) trans-membrane peak pressure of 8 psi (over 400mm Hg) and with 43% of the cycle at greater than 2 psig. The surrogate challenge virus was the bacteriophage  $\phi$ X174, which is 27nm in diameter. (Hepatitis B, which is the smallest known STD, is 42nm in diameter.) Nine hundred ml of buffer containing the challenge virus on the upstream (challenge) side contacted the inside of the device, while 212ml of buffer on the downstream side was assayed to detect and quantify any virus which penetrated the device.

Data from quantitative biological assays demonstrated that the test method, including the buffer, the components of the test apparatus, and the entire downstream side of the test setup, did not inactivate the challenge virus during the course of testing a sample device.

Reality™ devices that had laser-induced holes, which were partially characterized by scanning electron microscopy, were used as positive controls. The exit hole size was found to be smaller than the entrance hole size, and varied from sample to sample. Thus, the actual hole size was smaller than the nominal, "entrance", hole size. Virus penetration was determined for devices containing laser-induced holes with nominal sizes of 10, 20, 25 and 100µm. Different nominal 10µm holes allowed an average penetration of 2300nl (range: 520-4100nl) of the challenge virus suspension at 30 minutes.

b. Test Results with Intact Reality™ Devices

Fifteen Reality™ devices were tested with at least 4 samples from 3 different manufacturing lots. The results demonstrated that:

- 8 samples had no detectable virus penetration;
- 6 samples had apparent low-level virus penetration; and
- 1 sample had substantial virus penetration.

Of these 15 samples, there were two samples with evidence of virus contamination during assay and confirmed by reassay. This contamination did not interfere with conclusions regarding virus penetration of the devices.

Of the 6 devices with apparent low-level viral penetration, two cases were confirmed by reassay. Because of statistically low numbers of viral penetration, the other four could not be confirmed. The virus titers in the downstream buffer were indicative of 2-20nl penetration by the challenge virus suspension. One device allowed a higher level of virus penetration which increased with time during the test. The level of virus titer indicated virus penetration from a  $\geq 10\mu\text{m}$  hole.

Tests for virus penetration were also performed with three latex male condoms (with appropriate test system modification for the smaller diameter male latex condoms). These data indicated that no virus penetration was found in those samples.

c. Conclusions

The barrier properties of Reality™, with respect to sexually transmitted diseases, were analyzed in an artificial, laboratory test with a very small surrogate virus ( $\phi\text{X174}$ ). Eight devices allowed no detectable virus penetration; six allowed low level penetration, which given the test conditions, should represent

insignificant virus penetration in actual use. Overall, 14 of 15 devices were significant barriers to virus penetration.

#### 4. Quality Assurance Control Procedures

As an in-line production quality assurance (QA) test, every Reality™ device is tested to detect any pinholes. Helium is introduced into the device's interior and testing for helium is done on the outside environment. Detection is done using a commercially available detector (Mark model 9822) and a custom made holder for Reality™. Validation studies, using 120 devices with laser-induced holes of known sizes at various locations, demonstrated that this test is capable of detecting virtually all pinholes of 20µm or greater, (and most 10µm diameter pinholes) as close as 5mm from the outer ring of the device. This QA procedure is adequate to detect any degradation in manufacturing processes, and to assure the integrity of the device materials with respect to possible pinholes. This QA procedure compares favorably with QA procedures used for latex male condoms.

At end stage manufacture, Reality™ devices are checked with a defined sampling plan for leaks with a test similar to a standard ASTM test for latex male condoms. The devices are filled with water and visually checked for leaks in both vertical and horizontal orientations. Validation studies were conducted with over 600 devices with laser-induced holes at various locations. These studies demonstrated that the test is capable of detecting approximately 90% of 20µm diameter pinholes and over 50% of 10µm diameter pinholes, at locations greater than 30mm from the outer ring of the device. This QA procedure is adequate to assure the integrity of the device materials with respect to pinholes, and is comparable to the water leakage test used for latex male condoms.

#### B. Summary of Clinical Investigations

In response to the urgent public health need for a female barrier devices with the potential to prevent a life threatening disease, HIV infection, the Food and Drug Administration (FDA) developed an expedited study protocol. This expedited study protocol was made available to the public on April 4, 1990, in the form of a guideline entitled "Premarket Testing Requirements for Female Barrier Contraceptive Devices Also Intended to Prevent Sexually Transmitted Diseases". Because of the difficulties in studying STD prevention in clinical studies, the guideline designated pregnancy as a surrogate study endpoint if preclinical laboratory studies demonstrated that the device was an effective barrier to STD-sized particles. To further expedite the approval of such devices, a comparable historical control could be used. The Reality™ device was the first device reviewed by FDA since the development of these guidelines.

The clinical investigations summarized below establish the safety and effectiveness of Reality™. (Some early clinical investigations on prototype devices and data from countries outside the United States and Latin America are not reported below.)

1. Phase I - Dislodgement Study

- a. Study Methods - Study subjects were monogamous sexually active couples not at risk for pregnancy due to oral contraceptive use or sterilization. Each couple used 3 Reality™ devices and 3 latex male condoms in a pre-determined sequence. Study subjects completed a questionnaire on device dislodgement, breakage and acceptability after each use.
- b. Study Population - Fifty couples were enrolled in the study. A total of 49 couples completed the study for a total of 147 uses of Reality™ and 147 uses of the latex condom.
- c. Study Results - Study subjects reported all results by questionnaire. One Reality™ device and one latex condom broke during use (0.7%). Reality™ invaginated (i.e., the outer ring of the device was pushed inside the vagina) 26 out of 147 uses (17.7%), and the latex male condom slipped down the shaft of the penis 12 out of 147 uses (8.2%). There were 80 out of 147 uses where inserting Reality™ was difficult or impossible. Significant discomfort was reported for 19/147 (12.9%) and 1/146 (0.7%) uses of Reality™ and latex condoms, respectively.

The breakage, acceptability and dislodgement rates for Reality™ are considered adequate for a female barrier contraceptive device.

Phase 1 - Breakage Study

- a. Study Methods - Study subjects were monogamous sexually-active couples not at risk for pregnancy due to oral contraceptive use or sterilization. Each couple used 5 Reality™ devices and 5 latex male condoms in a pre-determined sequence. Within 12 hours after use, each device was returned via a mail pack and tested via the water leakage test. Study subjects also completed a questionnaire on device dislodgement, breakage and acceptability after use.
- b. Study Population - A total of 53 couples were enrolled in the study, and 44 couples completed the study. One couple discontinued due to partner dislike; 1 due to irritation to both devices; and 7 for personal reasons not related to either test product.
- c. Study Results - There were a total of 471 returned devices, including 237 Reality™ devices and 234 latex condoms. Of the returned devices, 6/237 (2.5%) Reality™ devices and 11/234 latex condoms were not testable (e.g., ripped or torn). Of the testable devices, 2/231 (0.9%) Reality™ devices failed the water leakage test and 5/223 (2.2%) latex condoms failed the water leakage test.

Study subjects reported 61/237 (25.7%) and 33/234 (14.1%) instances, respectively, where inserting Reality™ and the latex condom was difficult or impossible. Study subjects reported significant

discomfort for 11/234 (4.7%) and 13/233 (5.2%) uses of Reality™ and latex condoms, respectively.

The breakage rates and acceptability of Reality™ are considered adequate for a female barrier contraceptive device.

3. Phase 1 - Post Coital Sperm Test Study

- a. Study Methods - This study was conducted at the University of Chicago OB-GYN Outpatient Clinic. Study subjects were not at risk for pregnancy due to oral contraceptive use or sterilization. Study subjects underwent examinations for the presence of sperm in the vaginal vault upon entering the study and within 8 hours after use of Reality™. Study subjects were to use 5 lubricated Reality™ devices and were supplied an additional lubricant with spermicide.
- b. Study Population - Twenty-two study subjects were enrolled in the study, and five were lost to follow-up. Two study subjects used the device for one coital act, and discontinued the study. A total of 15 study subjects completed the study. In one coital episode, the partner failed to achieved ejaculation, leaving a total of 76 evaluable coital episodes.
- c. Study Results - Out of the 76 evaluable coital episodes, sperm was found in the vagina once (1.3%). However, this study subject reported improper use of Reality™, which may have caused this finding. These data are considered adequate for a female barrier contraceptive device.

4. Phase I - Vaginal Trauma Study

- a. Study Methods - This study was conducted at the Medical College of Virginia. Study subjects were not at risk for pregnancy due to oral contraceptive use or sterilization. Study subjects were randomly assigned to use Reality™ or the diaphragm. At the initial and follow-up visits, the vagina, cervix, and vulva of each participant were examined coloposcopically and aerobic, anaerobic, and fungal cultures of the vagina were taken. After the initial visit, study subjects were examined 3 hours post device wear (visit 2), post intercourse and overnight wear (visit 3), and post 7 day-use with a minimum of 5 coital episodes using the device (visit 4).
- b. Study Population - Thirty study subjects were enrolled in this study and randomly assigned to use Reality™ or a diaphragm. Fifteen subjects were randomized to each arm.
- c. Study Results - There was no evidence of significant trauma associated with the use of either contraceptive device. However due to the sample size, low frequency vaginal trauma due to device usage would not be expected to be detected. The resident vaginal flora did not significantly change during the three follow-up visits in study subjects using Reality™. Among diaphragm users, lactobacilli

were less frequently isolated at the third and fourth follow-up visits compared to the initial visit. Also, aerobic Gram negative rods were more frequently isolated at the fourth visit of diaphragm users.

5. Phase II - Trichomonas Reinfection

- a. Study Methods - This study was conducted at six trial sites: University of Chicago, Chicago, Illinois; Medical College of Virginia, Richmond, Virginia; University of Southern California, Los Angeles, California; Georgetown University, Washington D.C.; Yale University, New Haven, Connecticut; and Hahnemann University, Philadelphia, Pennsylvania. Study subjects were sexually active women at least 18 years of age with documented vaginal trichomoniasis. Study subjects were excluded if they relied upon another barrier contraceptive, were pregnant or had a clinical diagnosis of pelvic inflammatory disease.

All subjects were treated with a single 2 gram oral dose of metronidazole while in the physician's office. They were advised about the risk of reinfection, offered to have their partners evaluated and treated, and counseled that barrier protection should be used to protect against reinfection.

Each study subject was shown Reality™ and asked if she would use it every time she had intercourse during the study period (45 days). If she responded that she would be compliant, the subject was enrolled in the User group. If the subject felt that she would not be compliant, she was enrolled in the Control group. The User group was instructed to use Reality™ with each act of intercourse over the next 45 days. All subjects kept a diary of the number of their coital episodes.

- b. Study Population - One-hundred twenty six (126) subjects were entered into the study. Of these, 22 subjects did not satisfactorily complete the study for the following reasons: 19 (12 Controls, 7 Users) were lost to follow up; 2 Users did not have sexual intercourse during the study period; and 1 User reported that her partner used male condoms at the same time as she used Reality™. One-hundred four (104) subjects completed the study, 50 in the Control Group and 54 in the User Group.
- c. Study Results - Of the 54 study subjects who selected to use Reality™, only 20/54 (37%) reported compliant use (i.e., used Reality™ correctly during every coital act) while 34/54 (63%) reported non-compliant use. Trichomonas reinfection rates at the end of study were 7/50 (14%) for the Control Group, 5/34 (15%) in the Non-Compliant User Group, and 0/20 (0.0%) in the Compliant User Group. Although there was a lower rate of reinfection in the Compliant User Group, this difference was not statistically significant ( $\alpha=.05$ ).

6. Phase II - Pregnancy Use Effectiveness Study

- a. Study Methods - This study was conducted at nine trial sites, six in the United States and three in Latin America: Valley Center for Women's Health, Sacramento, California; Eastern Virginia Medical School, Norfolk, Virginia; Robert Wood Johnson Medical School, New Brunswick, New Jersey; Wayne State University Hospital, Detroit, Michigan; University of Arizona, Tucson, Arizona; Phoenix Baptist Medical Center, Phoenix, Arizona; Instituto de Investigacion Cientificia, Durango, Mexico; Clinica Evangelina Rodriguez Profamilia, Santo Domingo, Dominican Republic; and Hospital General de Veracruz, Veracruz, Mexico.

Study subjects were women between the ages of 18 and 40 who were in a monogamous relationship and reported frequent sexual intercourse (>2/week). Exclusion criteria included (1) any evidence of pelvic inflammatory disease, (2) pregnancy, (3) allergy to vaginal lubricants, (4) history of toxic shock syndrome, (5) Class III or IV Pap smear within 6 months prior to entry to the study, (6) history of infertility, (7) evidence of urinary tract infection, (8) symptoms of an STD, and (9) any contraindications to becoming pregnant.

Upon entering the study, all study subjects received a pelvic examination including a chemical pregnancy test, verbal instructions on use of Reality™ and on the coital log book, and sufficient supplies of Reality™. Follow-up visits were scheduled for 1, 3 and 6 months. At the 1, 3 and 6 month follow-up visits, study subjects underwent pelvic exams and reported product use history. At the 6 month follow-up visit or at the discontinuation visit, study subjects also had a Pap smear, chemical pregnancy test and completed the acceptability questionnaire. Two weeks after the 6 month follow-up visit, study subjects were to return for an additional chemical pregnancy test. Each study subject was instructed to contact the clinic if her menstrual period was overdue or any medical problem arose.

- b. Study Population - A total of 377 women were enrolled into this study. Table 1 shows the number of women enrolled in the study, ineligible for the study and lost to follow-up for the United States (U.S.) and Latin American (L.A.) centers.

Table 1. Study Population.

Enrollment Summary	U.S. Study Subjects	L.A. Study Subjects
Total Enrolled	262	115
Lost to Follow-Up	16	2
Protocol Exclusions	21	2
Total Study Subjects	225	111

Study subjects were considered to have completed the study if (1) they returned for the 6-month follow-up visit, (2) they had not discontinued using Reality™ prior to the 6-month visit and (3) the 6-month follow-up visit occurred at least 168 days after admission. Study subjects discontinued or reached a study endpoint for the following reasons: personal, accidental pregnancy, medical reasons, planned pregnancy and lost to follow-up.

Of the 225 women enrolled in the U.S., 147 (65.3%) women completed the study without a discontinuation or endpoint event. Of the 111 women enrolled in Latin America, 47 (42.3%) completed the study without a discontinuation or endpoint event. Reasons are listed below.

Table 2. Study Subject Endpoint and Discontinuation Events.

	U.S. Study Subjects	L.A. Study Subjects
Completed Study	147 (65.3%)	47 (42.3%)
Discontinued	78 (34.7%)	64 (57.7%)
Personal Reasons	46	35
Unplanned Pregnancy	22	17
Medical Reason	4	3
Planned Pregnancy	1	4
Lost to Follow-Up	5	4
Unknown	0	1
Total	225	111

c. Study Results

1. Safety - Adverse Effects

Safety data were analyzed for all women (359) who received Reality™ and returned to the clinic for the Month 1 Visit. During follow-up, 83 women (23%) reported newly occurring medical problems or conditions (not present at admission). Many of these medical conditions were systemic in nature (cardiovascular, digestive, endocrine, musculoskeletal, nervous and respiratory systems), and probably unrelated to device usage.

The following urogenital adverse effects were reported, and may or may not be related to device usage.

- a. Changes in Cervical Cytology - Gynecological exams and Pap smears were performed on all study subjects at the initial visit, at the 6-month visit and at the final visit. During follow-up, 2 study subjects with normal Pap smears at admission had Class III dysplasia.
- b. Infections - Of the 359 study subjects, 11 (3.1%) had vaginitis (candida or monilia), 6 (1.7%) had cervicitis, 4 (1.0%) had urinary tract infections, 2 (0.6%) had cystitis, 1 (0.3%) had pelvic inflammatory disease, 1 (0.3%) had non-specific vaginitis and 1 (0.3%) had human papillomavirus infection.
- c. Irritation - One partner (0.3%) experienced irritation and erythema to the penis.
- d. Bleeding - One study subject (0.3%) reported intermenstrual bleeding/spotting.

The potential adverse effects stated above are considered acceptable for a female barrier contraceptive.

2. Effectiveness

Pregnancy rates for women using Reality™ were calculated using life table analysis. The 6-month gross cumulative life table pregnancy rates with standard error are shown in Tables 3 and 4. As seen in Tables 3 and 4, subsets of study subjects had higher 6-month gross cumulative pregnancy rates. For example, the 6-month pregnancy rate for Latin American women was 21.7% compared to 12.2% for the U.S. study subjects. The 6-month pregnancy rate for U.S. women less than 25 years of age was 21.4%. However, there were only a small number of women less than 25 years of age in the study.

Overall, there were a total of 39 pregnancies, 22 among U.S. study subjects and 17 among L.A. study subjects. Pregnancies were categorized as method or user failures by using (1) study subject's

reported history of product use during the study and (2) investigator's reported reason. Any reported non-compliance with use of Reality™ was defined as a user failure. Of the 39 pregnancies, 12 (30.8%) were attributed to methods failures; 6 due to mechanical/structure failure of the device (e.g., breakage, slippage) and 6 due to unknown causes.

The 6-month gross cumulative pregnancy rates listed in the lifetable analysis may slightly underestimate the true pregnancy rate for two reasons. First, there was a failure to discontinue several study subjects at the appropriate time in the lifetable due to infrequent sexual intercourse, as specified in the protocol. Second, a few study subjects had abnormal pelvic exams which may or may not affect their fertility. However, the effects of these protocol deviations will only slightly increase the cumulative pregnancy failure rate.

Direct statistical comparisons of the contraceptive effectiveness of Reality™ to other barrier methods, or historical controls, cannot be made for several reasons. First, there were significant differences between the study populations of historical controls and Reality™. These differences included important variables which may be associated with contraceptive use-effectiveness, for example, age and parity. Second, the study protocols differed between the historical controls and the Reality™ study.

Table 3. Gross Life-Table Pregnancy Rate for U.S. Study Subjects.

Time Months	Average at Risk	Number of Pregnancies	Monthly Failure Rate	Standard Error	Cumulative Failure Rate	Cumulative Standard Error
1	211.0	6	0.028	0.011	0.028	0.011
2	186.0	5	0.027	0.012	0.055	0.016
3	170.5	3	0.018	0.010	0.071	0.018
4	160.0	4	0.025	0.012	0.094	0.021
5	153.5	2	0.013	0.009	0.106	0.023
6	113.5	2	0.018	0.012	0.122	0.025

Table 4. Gross Life-Table Pregnancy Rate for L.A. Study Subjects.

Time Months	Average at Risk	Number of Pregnancies	Monthly Failure Rate	Standard Error	Cumulative Failure Rate	Cumulative Standard Error
1	100.0	6	0.060	0.024	0.060	0.024
2	79.0	2	0.025	0.018	0.084	0.028
3	69.0	3	0.044	0.025	0.124	0.035
4	59.0	2	0.034	0.024	0.153	0.040
5	53.5	4	0.075	0.036	0.217	0.048
6	44.0	0	0.000	0.000	0.217	0.048

Of the 225 U.S. study subjects, 86 were compliant users. A compliant user had the following characteristics: (1) never reported irregular use of Reality™, (2) did not use another method of contraception, (3) followed the instructions for use and (4) did not have fewer than four coital episodes during a month. The 6-month gross cumulative probability of a method failure among these compliant or "perfect" U.S. users is listed below.

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Table 5. Method Failure Rate Among Compliant  
U.S Study Subjects at 6-Months.

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Failure Rate	Standard Error
5.4	2.7

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#### 4. Acceptability

After completion or at the time of discontinuation, study subjects and their partners completed a questionnaire on Reality™ to assess its acceptability. The most frequently noted complaints were related to not liking the inner ring and movement of the device during use. Of the 302 women who completed the questionnaire, 208 (68.9%) reported that they did not have difficulty inserting Reality™ while 94 (31.1%) reported difficulty inserting Reality™. Of the 83 women in the Treated Population who discontinued using Reality™ for personal reasons, 21 (25%) discontinued because their partner didn't like using Reality™. Approximately 17% (14 out of 83 study subjects) discontinued because they disliked the method or feared pregnancy. Of the 83 study subjects who discontinued, 8 (10%) cited discomfort as the reason for discontinuation. The acceptability of Reality™ is considered adequate for a female barrier contraceptive device.

#### IX. Conclusions

The physical properties of Reality™, in terms of material strength, are adequate to meet the normal intended use of the device. The barrier properties of Reality™ with respect to sexually transmitted diseases were analyzed in an artificial, laboratory test with a very small surrogate virus (φX174). Eight devices allowed no detectable virus penetration; six allowed low level penetration, which given the test conditions, should represent insignificant virus penetration in actual use. Thus, 14 of 15 devices were significant barriers to virus penetration.

*In vitro* assays, acute animal studies and sub-chronic animal studies were performed on Reality™ to establish the safety of the device materials for their intended use. These studies revealed no evidence of cytotoxicity, dermal irritation, dermal sensitization, acute systemic toxicity or mutagenicity. Mild irritation was noted in the acute mucosal irritation test and in one of the

chronic irritation tests. A few study subjects did report irritation after using the device in the clinical investigations.

A series of clinical studies were conducted to evaluate potential adverse effects, device breakage, device displacement, acceptability, usage and comfort of the Reality™ device. These studies demonstrate that potential adverse effects, breakage, displacement and acceptability for Reality™ are adequate for its intended use.

The pregnancy use-effectiveness of Reality™ was evaluated in a single arm, multi-center clinical study for 6 months. The results of this study showed that Reality™ provided some barrier protection against pregnancy. The 6-month cumulative pregnancy rate for U.S. women was 12.2%. This rate slightly underestimates the true pregnancy rate because there was a failure to discontinue several study subjects at the appropriate time in the lifetable analysis due to infrequent sexual intercourse and a few study subjects had abnormal pelvic exams, which may affect their fertility. If these study subjects were removed from the lifetable analysis at the appropriate time, the 6-month pregnancy rate for Reality™ is expected to be approximately 13%. Because of the lack of a comparable control group, the extent of protection Reality™ provides against pregnancy compared to other barrier methods remains uncertain. The in vitro barrier properties of Reality™ combined with the pregnancy-use effectiveness data show that Reality™ should provide some barrier protection against STDs, including HIV infection, compared to using no method.

#### X. Panel Recommendations

The Obstetrics-Gynecology Devices Panel (the Panel) met on January 31, 1992, to consider the preliminary safety and effectiveness data on Reality™. At that time, less than one-half of the required study subjects had completed the pregnancy-use effectiveness study. At this meeting, the Panel unanimously recommended that the PMA be considered approvable subject to the submission and review of additional preclinical and clinical data, including completing the pregnancy-use effectiveness study.

On December 10, 1992, the Panel reconvened to consider the completed pregnancy use-effectiveness study and the device labeling for Reality™. Although the Panel expressed concern about the limited safety and effectiveness data and the high failure rate, the Panel voted unanimously to approve Reality™ subject to certain conditions because there is no other barrier method that women can use to protect themselves from STDs, including HIV infection, if their partners will not use latex male condoms. These conditions included the following: (1) limiting the safety and effectiveness claims, especially with respect to the prevention of HIV transmission (2) revise the patient labeling to reflect the limited data and (3) develop professional labeling. The Panel also recommended that the 12-month pregnancy rate could be estimated for Reality™ by approximately doubling the 6-month pregnancy rate.

## XI. FDA Decision

When evaluating the safety and effectiveness of Reality™, FDA considered the following relevant factors: (1) the persons for whom the device is intended; (2) the conditions of use for the device, including the conditions of use prescribed, recommended and suggested in the labeling of the device; (3) the lack of available alternatives for women whose partners do not use latex male condoms; and (4) the probable benefit to health from the use of the device weighed against any probable injury of illness from such use. FDA also considered and accepted, as a basis for approval, the use of pregnancy data as a surrogate for the prevention of STD transmission where *in vitro* tests demonstrated adequate barrier properties of the device.

Although the safety and effectiveness data were limited, FDA determined that Reality™ should provide some protection against both pregnancy and STDs, including HIV infection, for couples who do not use latex male condoms. Further, the public health benefits of some protection against HIV infection for couples not using latex condoms outweighed the limitations of available data.

In reaching this determination, FDA considered the urgent need for a means whereby women can help protect themselves from sexually transmitted diseases, including HIV infection, and the fact that the male latex condom is the only alternative. FDA also considered that couples who are currently using latex condoms, which are highly effective at preventing STDs if used properly, may choose to use Reality™ instead. Therefore, FDA determined that the labeling for the Reality™ must include a warning regarding the relative demonstrated effectiveness of the male latex condom for STD prevention compared to the limited data for Reality™. Finally, FDA considered the fact that the pregnancy-use effectiveness of Reality™ had not been tested as extensively as other new contraceptives, and that the contraceptive failure rate for Reality™ could not be statistically evaluated against one or more currently approved contraceptives, resulting in some uncertainty in the actual failure rate. However, after listening to public testimony at the December 10, 1992, Panel meeting on the need for Reality™ labeling to have a contraceptive claim to increase Reality's acceptability for use for prophylactic purposes, FDA determined that a limited contraceptive claim was in the public health interest.

Notwithstanding these issues, FDA still determined that the potential benefit of preventing HIV infection among couples who do not use latex condoms outweighed the possible risks provided that the device labeling accurately reflect the limited safety and effectiveness data. Therefore, FDA concurred with the recommendation of the Obstetrics-Gynecology Devices Panel subject to the applicant submitting additional preclinical and clinical safety and effectiveness data. The applicant amended the PMA on January 22, and 29, February 2 and 9, March 3, April 15, and May 6, 1993, to address the remaining preclinical and clinical deficiencies and revise the device labeling.

The applicant has concurred with the conditions of approval. These conditions included the following: (1) confirming the barrier properties of Reality™ by repeating the  $\phi$ X174 Bacteriophage studies on devices made from mass production lots, (2) conducting real-time aging studies to establish the device shelf-life, (3) developing professional labeling, (4) conducting focus-group studies to

refine the patient labeling, and (5) participate in future government sponsored studies of Reality™.

On-site inspection on January 25 and April 15, 1993, found the applicant's manufacturing facility to be in compliance with the device Good Manufacturing Practice Regulations.

FDA has determined that, based on data submitted in the PMA, there is reasonable assurance that Reality™ is safe and effective for its intended use, and issued an approval order on MAY 7 1993.

## XII. Approval Specification

Directions for Use: See the Labeling (Attachment 1).

Warning, Hazards to Health for Use of the Device: See indications, contraindications, warnings, precautions and adverse effects in the labeling (Attachment 1).

Post-Approval Requirements and Restrictions: See approval order (Attachment 2).

A copy of the final labeling and all subsequent changes to the labeling approved by CDRH may be reviewed at the Food and Drug Administration, Center for Devices and Radiological Health, 1390 Piccard Drive, Rockville, Maryland 20850.

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# United States Patent [19] Hessel

[11] Patent Number: 4,976,273  
[45] Date of Patent: Dec. 11, 1990

[54] TUBULAR PROTECTIVE DEVICE FOR PROTECTION AGAINST TRANSFER OF INFECTIOUS MATTER DURING SEXUAL INTERCOURSE

[75] Inventor: Lasse Hessel, Goring-On-Thames, England

[73] Assignee: Chartex International plc, London, England

[\*] Notice: The portion of the term of this patent subsequent to Apr. 5, 2005 has been disclaimed.

[21] Appl. No.: 148,992

[22] Filed: Jan. 27, 1988

## Related U.S. Application Data

[63] Continuation of Ser. No. 58,766, Jun. 15, 1987, Pat. No. 4,735,621.

## [30] Foreign Application Priority Data

Mar. 2, 1987 [DK] Denmark ..... 1075/87

[51] Int. Cl.: ..... A61F 13/00

[52] U.S. Cl.: ..... 128/844; 604/349

[58] Field of Search ..... 128/127, 128, 129, 130, 128/131, 132 R, 138 R, 830, 842, 844, 832; 604/327-331, 346-353

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Primary Examiner—Stephen C. Pellegrino

Attorney, Agent, or Firm—Levy, Zito & Grandinetti

## [57]

## ABSTRACT

A thin-walled, condom-like tubular protective device for protection against the transfer of infectious matter during sexual intercourse is disclosed. The condom-like device has an open end a collar-shaped outwardly extending portion with a ring-like member for radially stretching the collar and has an inner diameter which is sufficiently large to permit movement of a penis with respect to the protective device during coitus.

4 Claims, 2 Drawing Sheets

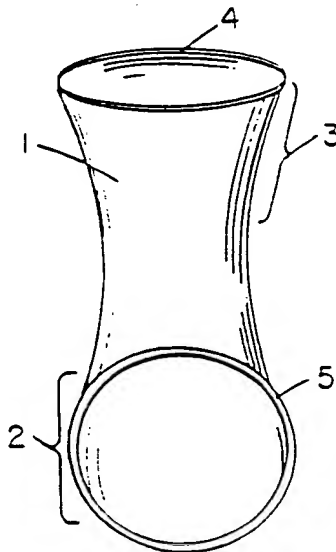


FIG. 1

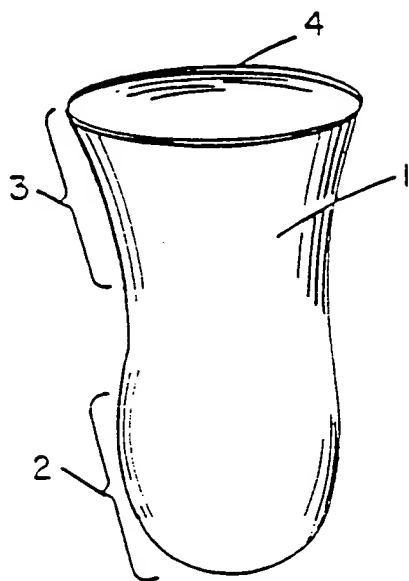
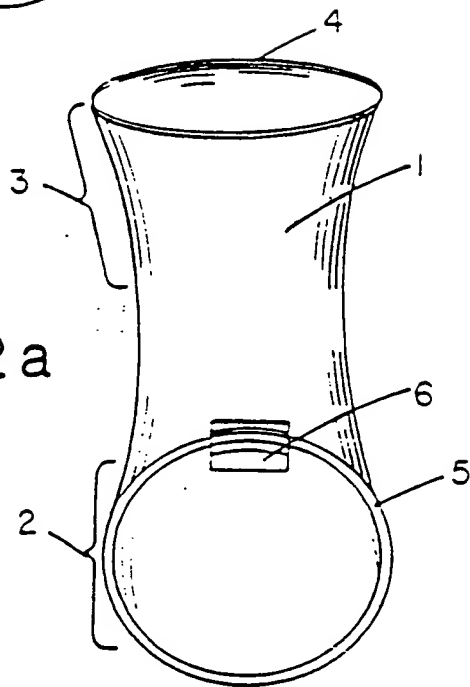
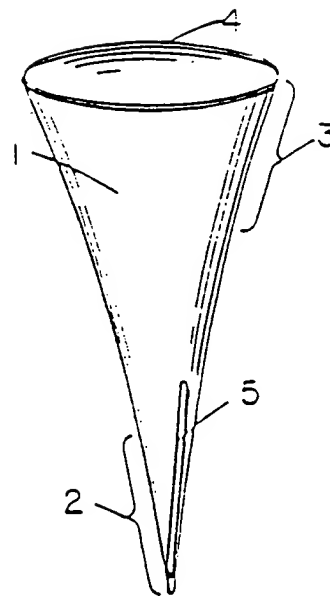
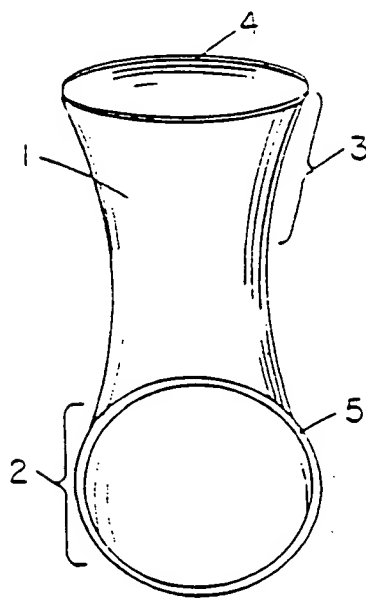
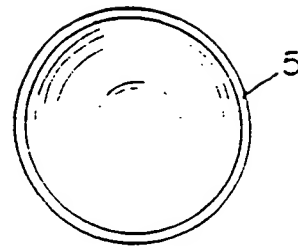
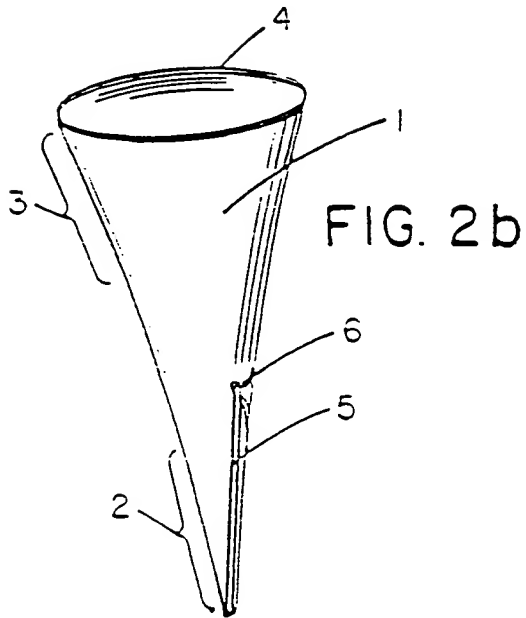


FIG. 2a





# TUBULAR PROTECTIVE DEVICE FOR PROTECTION AGAINST TRANSFER OF INFECTIOUS MATTER DURING SEXUAL INTERCOURSE

This is a continuation of U.S. Pat. application Ser. No. 058,766, filed June 5, 1987, now U.S. Pat. 4,735,621.

## BACKGROUND OF THE INVENTION

### 1. Field of the Invention

The present invention relates to a tubular protective device or condom-like device for protection against the transfer of infectious matter during sexual intercourse. Specifically, the invention relates to a thin-walled tubular protective device having a closed end and an open end wherein the open end has an outwardly extending portion with means for keeping the open end radially stretched.

### 2. Description of the Background Art

Condoms, besides being contraceptives, offer protection during sexual intercourse against the transfer of infectious matter such as bacterial and viral microbes that cause venereal diseases. After the appearance of AIDS great efforts have been made by various health authorities to impel people to increase the use of condoms during sexual intercourse in order to prevent the spread of this fatal disease.

Condoms comprise a thin tubular casing, that is typically manufactured from latex and that has an open end and a closed end. Condoms are drawn over the penis before coitus. The casing has an inner diameter that is adapted to allow the condom to fit tightly on the penis. At the open end of a condom an elastic, flexible ring or rolled portion of latex is usually provided. This ring portion is the same diameter as the tubular casing of the condom. This elastic ring portion serves primarily to secure the condom on the penis and to prevent leakage of semen from the interior of the condom. Such elastic ring portions contract the open end of a condom onto the penis and do not radially extend the open end of the condom.

It is a generally accepted that the AIDS virus can only be transferred through contact with the carrier's blood or blood plasma. During sexual intercourse such a transfer of the AIDS virus occurs when lesions of the carrier contact the mucous membrane or skin of the carrier's partner. Such a transfer of the AIDS virus is especially likely to occur around the root or base of the penis and the vulva. There is a risk that lesions in these areas can be caused to bleed during sexual intercourse. When using a standard condom, these areas are unprotected or unshielded by the condom and consequently a condom does not offer full protection against the transfer of infectious matter such as the AIDS virus.

Numerous attempts have been made to design a condom or condom-like device that provides effective contraception and/or more protection against the transfer of infectious matter than the standard condom. A sampling of these attempts are described below.

U.S. Pat. No. 4,004,591 to Freimark discloses a birth control device. This birth control device is a female condom made of a strong rubber, plastic, or other similar material. This condom has a rigid, ring-like rim that is bent or scalloped. This rim can be a wire. The rim is not adapted to radially extend the open end of this device because this device is a hard molded material and not flexible. The cross-sectional dimensions of this con-

dom are disclosed as being sufficiently large to easily accommodate the average male width with some additional clearance space. The primary function of this device is to prevent unwanted pregnancy. This device is useful in preventing the spread of venereal disease. This device provides no means to prevent an exchange between partners of secreted fluids that may contain venereal disease. Additionally, this birth control device is intended for use by females, but includes no means to secure or maintain the device in the vagina.

U.S. Pat. No. 4,630,602 to Strickman et al. discloses a disposable contraceptive cervical barrier. The cervical barrier of this invention is similar to standard diaphragms in size and design. This cervical barrier contains various "cavities for cells" that can hold spermicidal lubricants. These spermicidal lubricants can also be placed in numerous grooves within the body of the cervical barrier. Urethane polymers are used to make the device. The cervical barrier of this invention, unlike a condom, has no tubular side walls to prevent the exchange between partners of secretions that can contain a venereal disease.

U.S. Pat. No. 3,536,066 to Ludwig discloses a human birth control appliance. The appliance of this patent protects both partners from any dermic contact. This device is large and awkward to use.

U.S. Design Pat. No. 254,808 to Meidahl discloses a design for a male contraceptive. This contraceptive appears to be larger in diameter than the average condom, but this contraceptive has no means at its open end to aid in the prevention of the spread of venereal disease.

The industry is lacking a simple, easy-to-use device that provides protection against the transfer of body fluids between partners during sexual intercourse, especially between the base of the penis and the vulva.

## SUMMARY OF THE INVENTION

The invention is a tubular protective device for protection against a transfer of infectious matter during sexual intercourse. The protective device comprises a flexible, thin-walled, tube that is closed at one end and has at an open end a collar-shaped, outwardly extending portion with means for radially stretching the collar or open end. The inner diameter of the device is sufficiently large to permit movement of a penis with respect to the tubing of the device during coitus or sexual intercourse.

A desirable embodiment of the invention is a tubular protective device that comprises a flexible, thin-walled tube having a closed end, an open end, and a first diameter. This embodiment of the invention further has an outwardly extending collar-shaped means of a second diameter for radially stretching the open end wherein the first diameter of the tube is smaller than the second diameter of the means for radially stretching and the first diameter is sufficiently large to permit movement of a penis within the tube of the device during sexual intercourse.

A desirable embodiment of the invention, that is adapted to function as a female condom like device, is a tubular protective device that comprises a flexible, thin-walled tube having a closed end and an open end. This embodiment also has a first outwardly extending ring-shaped means that is adapted for radially extending the open end and a second outwardly extending ring-shaped means that is adapted for radially extending the closed end. The second ring-shaped means secures or

maintains the device in the vagina in a manner similar to a diaphragm.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a three dimensional view of the protective device of this invention.

FIG. 2a is a three dimensional front view of the invention that is adapted to function as a female condom-like or protective device.

FIG. 2b is a three dimensional side view of the protective device of FIG. 2a.

FIG. 3 is a top plan view of a closed end or internal ring for use with the protective device of FIG. 1.

FIG. 4a is a three dimensional front view of the protective device of FIG. 1 with the closed end or internal ring of FIG. 3 inserted therein.

FIG. 4b is a three dimensional side view of the protective device of FIG. 1 with the closed end or internal ring of FIG. 3 inserted therein.

### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention is a tubular protective device for protection against a transfer of infectious matter during sexual intercourse. The device comprises a flexible, thin-walled tube closed at one end and open at a second end. The open end has a collar-shaped, outwardly extending portion and a means for radially stretching the collar-shaped portion or open end. The device has an inner diameter of sufficiently large dimension to permit movement of a penis with respect to the protective device during sexual intercourse. Besides protecting against a transfer of infectious matter, the protective device is a contraceptive and, due to the presence of the collar-shaped portion of the device, the contraceptive effect is even more efficient than that obtained with standard condoms because of the additional protection provided around the vulva.

The invention is based on the discovery that a particularly good protection against the transfer of infectious matter, and especially the AIDS virus is obtained if a condom-like or tubular protective device is used during sexual intercourse that has at its open end an outwardly extending collar that is connected to a rigid ring-like means. The ring-like means is adapted to maintain the collar of the device in a radially extended or stretched condition. The collar is preferably of a dimension that covers the vulva completely. The tubular protective device desirably has a sufficiently large inner diameter to allow movement of a penis with respect to the walls of the tubular device. The walls of the tubular device are held in a relatively immovable state or condition against the vaginal wall. The collar covering the vulva is, also, essentially immovable with respect to the vulva during coitus.

The flexible, thin-walled tube of the invention is desirably cylindrical in shape and has an open end and a closed end. The tube is preferably made from a natural or synthetic polymer material. Desirable polymer materials are members selected from the group consisting of latex, polyethylenes, polyurethanes, and derivatives based upon these polymers. The preferred material is a polyether polyurethane that has a soft, nonadhesive "hand feel". Other polymers or plastics such as polyolefins can be used to manufacture the tube of this device.

The tube of this device can be manufactured by numerous methods that are standard within the industry that fabricates items from polymer materials. The par-

ticular method chosen to manufacture the device of this invention varies with the particular polymer material chosen. An acceptable method of manufacturing the device can include curing a polymer material, such as latex, on a mold that has been dipped into a container of heated, liquified polymer material. Other methods can include either vacuum forming or blow molding a sheet of heated polymer material into or onto a mold. Vacuum forming and blow molding are desirable with synthetic polymer materials such as polyurethanes.

The preferred method for manufacturing the device, when it is made of a synthetic polymer such as polyurethane, is to heat seal two layered sheets of the polymer material together to form the desired shape of the device. Heat sealing methods can be undesirable if caution is not exercised during the process. This is because these methods can leave hardened seams that can potentially irritate skin and mucous membrane surfaces. Additionally, the seams are subject to leakage and tearing if the heat sealing method is performed at an undesirably high temperature. Heat sealing methods, however, are desirable because the sheets of polymer material is not stretched during the manufacturing of the device and a consistent wall thickness for the device can be obtained.

The wall thickness of the condom-like device can vary greatly. Typically, thinner wall thicknesses for the device allow more sensitivity during coitus. Wall thicknesses can be varied depending upon the strength of the polymer material that is chosen for the device. Preferably, a wall thickness for the device is between 20 and 60 microns ( $\mu\text{m}$ ) for synthetic materials such as polyurethanes and 30 to 90 microns for natural materials such as latex. A wall thickness, regardless of the material from which the device is manufactured, must provide a tensile strength of at least 17 MPa when tested less than 12 months after manufacture and at least 15 MPa when tested 12 months or more after manufacture in order to comply with the standards of the American Society for Testing and Materials.

The internal or inner diameter of the tubular protective device in its unstretched state is desirably of a sufficiently large dimension to permit movement of a penis with respect to the protective device during sexual intercourse. The invention can have an inner diameter that causes the condom to be form fitting, but form fitting condom devices do not permit adequate sensitivity for the male during sexual intercourse. This is because a form fitting condom moves with the penis and prevents direct contact between the vaginal wall and the gians area during intercourse. This undesirable effect of form fitting condoms discourages their use by many members of the public. A condom-like device having a large inner diameter merely functions as a liner for the vaginal wall. In this situation the device is relatively stationary to the vaginal wall and the gians is in direct contact with the surface against which it is moving. This structural arrangement, wherein the inner diameter of the condom-like device is larger than a penis, provides greater sensitivity for both partners.

Desirably any diameter of the tube below the outwardly extending collar-shaped means for radially stretching the open end, such as an elastic ring, is smaller than a second diameter of the means for radially stretching the open end and the first diameter is sufficiently large to permit movement of a penis within the tube during sexual intercourse.

Standards within the industry for condoms, typically, do not define the inner diameter of a condom, but define

the acceptable width of the condom when it is laid flat on a surface. A condom having a width of about 47 millimeters to about 51 millimeters is considered, within the industry, to be form fitting. Contoured or loose fitting condoms have a width of about 50 millimeters to about 54 millimeters. For this invention an acceptable width is at least about 50 millimeters in an unstretched state along the entire length of the tube. A desirable range for the width of the condom-like device of this invention is between about 55 millimeters and about 85 millimeters.

The collar-shaped, outwardly extending portion of the protective device has a means for radially stretching or extending the collar, such as a ring. Furthermore, the ring serves to prevent the open end of the tubular protective device from being pushed into the vagina during sexual intercourse.

The means for extending the collar is desirably a semicircular ring or ring-like member. In the most desirable embodiments of the invention, the ring is manufactured from a suitable plastic as a separate part. The invention can be made wherein the means for extending the collar is integrally formed from the same material from which the walls of the device are formed. Such a structure can be formed by rolling the polymer material that forms the walls of the device from the open end of the tube so as to form a ring of material. This ring of material can be maintained by heating the ring or using an adhesive to maintain the ring and prevent it from unrolling.

The diameter of the means for radially stretching the collar is desirably large enough to prevent the exchange of secretions between partners during sexual intercourse. The diameter of the means for radially stretching the collar is desirably large enough such that the vulva and the base of the penis are covered by the extended collar. The preferred embodiments of the invention have a first diameter for the tube of the device and a second diameter for the means for radially stretching the collar such as an elastic ring wherein the second diameter is larger than the first diameter. Acceptable diameters for the means for radially stretching the collar of the device are at least about 50 millimeters and desirably between about 60 and about 75 millimeters. Preferably, the collar is conically shaped and when a tubular protective device having an inner diameter of approximately 50 millimeters is used the collar, supported by the means for radially stretching, preferably has an inner diameter of approximately 75 millimeters.

Insertion into the vagina of the tubular device of the invention can be done by either the man or the woman. The device can be inserted in the traditional manner by the male partner placing the device over the penis before coitus. The female partner can insert the device with a finger or by means of an insertion probe or applicator.

In order to prevent the tubular protective device from unintentionally slipping out of the vagina once inserted by the female partner has occurred, a means for retaining the device in the vagina such as a circular elastic member or an elastic ring can be used. This member or ring can be connected to the internal or external wall at or near the closed end of the device. After being placed correctly in the vicinity of the uterus, the circular elastic member or an elastic ring is maintained within the vagina in the same manner as a diaphragm.

In order to facilitate insertion of the tubular protective device into the vagina, the closed end of the device

can be enclosed by a sheathing which is axially movable relative to the protective device. During the insertion of the protective device into the vagina, the sheathing is moved backwards and, thus it opens for insertion of the closed end of the protective device. Such a sheathing is not typically present if a means for retaining the device in the vagina such as an elastic ring is present.

Prior to or in connection with the insertion of the tubular protective device, a lubricant is preferably applied to at least the inner side of the device to reduce friction during contact with the penis. If desired, a lubricant can also be applied to the exterior side of the device. Application of a lubricant to the inner side of the tubular protective device can facilitate the insertion of the device into the vagina. Selection of a desirable lubricant can vary greatly. The selection of a lubricant depends in part upon the compatibility of the lubricant with the polymer material used to manufacture the device. Desirable lubricants can include ointments, creams, or water-based mucilages or mucilage-like substances such as cellulose-based lubricants.

The invention is described in more detail with reference to the figures which show desirable embodiments of both the male and female tubular protective devices according to the invention.

FIG. 1 discloses a thin-walled tubular device 1 having a closed end 2 that is rounded. At the end of the thin-walled tubular device 1 that is opposite to the closed end 2, the thin-walled tubular device 1 continues into a conically-shaped collar 3 ending in an elastic ring 4. The composition and dimensions of the elastic ring 4 are adapted such that the collar 3 is stretched and maintained in a stretched condition. The flexible material used to form the thin-walled tubular device 1 of this embodiment overlaps or encapsulates the elastic ring 4. The thin-walled tubular device of this figure functions as a male condom-like device.

FIG. 2a discloses a front view of a thin-walled tubular device 1 having a closed end 2, that is rounded, and a collar 3 that is stretched by an elastic ring 4. At the rounded end 2 the thin-walled tubular device 1 a second elastic ring 5 is located and held in position by a means for affixing the ring 6. In this figure the means for affixing the ring is a small square of flexible material that is affixed on two of its edges to the thin-walled tubular device 1. In this manner the small square of flexible material is adapted to allow the second elastic ring 5 to pass freely through an open passage between the center of the square of flexible material and the thin-walled tubular device 1 that is covered by the square of flexible material 6. The means for affixing the ring serves to maintain the thin-walled tubular device 1 in the vagina. The thin-walled tubular device of this figure functions as a female condom-like device.

In FIG. 2a the tubular element 1 can be enclosed at the closed end by a thin cylindrical sheathing (not shown) which is axially movable in relation to the tubular element 1. However, the tubular protective device does not ordinarily have both a sheathing and a second elastic ring 5 at the same time.

FIG. 2b discloses a side view of the thin-walled tubular device 1 of FIG. 2a. In this figure the structural and spatial arrangement at the closed end 2 of the second ring 5 and the square of flexible material 6 is depicted so as to illustrate the passage through which the second ring 5 is free to move. The second ring 5 in this embodiment is not in a planar position that is parallel to the planar position of the first ring 4. This planar position of

the second ring 5 is at an acute angle to the planar position of the first ring 4 in this embodiment because the opening of the uterus is positioned at a similar angle to the vulva.

The diameter of the internal or second ring 5 is typically smaller than the diameter of the first ring 4. The diameter of the second ring 5 can vary to include any size that can adequately maintain the closed end 2 in the vagina. In this manner the female condom-like device can be inserted into the vagina and worn for a significant period of time before coitus. Desirable outer diameters for the second ring 5 are those typically used for diaphragms which are between about 65 millimeters and 80 millimeters.

FIG. 3 is a top plan view of the internal or second ring 5 of FIG. 2b. In desirable embodiments of the invention the second ring 5 is not attached to the flexible wall of the thin-walled tubular device 1. In such embodiments the thin-walled tubular device of FIG. 1 can be provided with, but separately from, the second ring 5. In this manner the invention can be adapted for use either as a male or female condom-like device after its purchase. The thin-walled tubular device 1 can be used as a male condom-like device without a second ring 5. The thin-walled tubular device 1 can be adapted for use as a female condom-like device by inserting the second ring 5 into the closed end 2 of the thin-walled tubular device 1.

FIG. 4a depicts a front view of the thin-walled tubular device 1 of FIG. 1 with the internal or second ring 5 of FIG. 3 inserted into the closed end 2. This represents the preferred embodiment of the invention. The second ring 5 is inserted into the closed end 2 by squeezing it to form an oval shape and then inserting the second ring 5 into the thin-walled tubular device 1. When the second ring 5 is released, it regains its circular shape. When the second ring 5 is in place, the thin-walled tubular device 1 can be inserted into the vagina by using the second ring 5 to function in a manner similar to a diaphragm.

FIG. 4b depicts a side view of the thin-walled tubular device 1 of FIG. 1 with the internal or second ring 5 of FIG. 3 inserted into the closed end 2.

I claim:

1. A tubular protective device for protection against a transfer of infectious matter during sexual intercourse consisting of:

- (a) a flexible, thin-walled tube having a sufficiently large first diameter to permit movement of a penis within said tube during coitus, said tube having a closed end and an open end, said open end having:
  - (i) a collar-shaped, outwardly extending conical portion, and

- (ii) an elastic ring integrally connected with said collar-shaped portion having a second diameter larger than said first diameter; wherein said flexible, thin-walled tube is a polymer material, said polymer material being selected from the group consisting of polyethylenes, polyurethanes, and derivatives thereof; and

- (b) a means for retaining located in said closed end of said flexible, thin-walled tube and having a diameter sufficient to maintain said means for retaining in a vagina of an user.

2. A tubular protective device for protection against a transfer of infectious matter during sexual intercourse, said protective device consisting of:

- (a) a thin-walled, flexible tube having:
  - (i) a closed end,
  - (ii) an open end, and
  - (iii) a first diameter sufficiently large to permit movement of a penis within said tube during coitus;

- (b) an outwardly extending collar-shaped means for radially stretching said open end, said collar-shaped means having a second diameter larger than the first diameter and attached to the open end of the tube;

wherein said flexible, thin-walled tube is a polymer material, said polymer material being selected from the group consisting of polyethylenes, polyurethanes, and derivatives thereof; and

- (c) a means for retaining located in said closed end of said flexible, thin-walled tube and having a diameter sufficient to maintain said means for retaining in a vagina of an user.

3. The tubular protective device of claim 2 wherein said means for retaining is affixed to said flexible, thin-walled tube.

4. A tubular protective device for protection against a transfer of infectious matter during sexual intercourse comprising:

- (a) a flexible, thin-walled tube having a sufficiently large first diameter to permit movement of a penis within said tube during coitus, said flexible thin-walled tube having a closed end, and an open end, said open end having:

- (i) a collar-shaped, outwardly extending portion; and
- (ii) a first elastic ring integrally connected with said collar-shaped portion having a second diameter larger than said first diameter;

- (b) a means for retaining located in said closed end of said flexible, thin-walled tube and having a diameter sufficient to maintain said means for retaining in a vagina of an user.

• • • • •

received  
10/20/92



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

Karen Lee Orzechowski  
Karen Lee Orzechowski  
LEVY, ZITO & GRANDINETTI  
1910 K Street, N.W., Suite 411  
Washington, DC 20006-1104

Re: Status Regarding Certificate of Correction for  
U.S. Patent No. 4,976,273

Dear Karen Lee Orzechowski

On June 1, 1992, we received a request for a Certificate of Correction for the above-referenced patent. We are currently experiencing a backlog of approximately 6-8 months. We appreciate your patience while we work through our backlog.

Should expedited services be required, please contact me at (703) 305-8127.

Sincerely,

Mary Allen, Manager  
Certificates of Correction Branch  
Office of Publication and Dissemination

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor : HESSEL, Lasse  
Patent Number : 4,976,273  
Serial Number: : 07/148,992 (Filed January 27, 1988)  
Issue Date : December 11, 1990  
For : TUBULAR PROTECTIVE DEVICE FOR PROTECTION  
AGAINST TRANSFER OF INFECTIOUS MATTER  
DURING SEXUAL INTERCOURSE

REQUEST FOR CERTIFICATE OF CORRECTION

The Honorable Commissioner  
of Patents and Trademarks  
Washington, D.C. 20231

Sir:

Please issue a Certificate of Correction for the above-identified patent correcting the errors listed on the enclosed PTO Form-1050.

The errors in the issued patent include mistakes incurred through the fault of the U.S. Patent and Trademark Office. These mistakes include mistakes that are of a nature that the meaning intended is not obvious from the context, and thus should be subject to a Certificate of Correction. These mistakes which are the fault of the U.S. Patent and Trademark Office are listed below:

In the Related U.S. Application Data, line 1, "Jun. 15, 1987" should read --Jun. 5, 1987--;

In the Other Publications, line 4, "1934," should read --1934),--;

In the Other Publications, line 7, "condoms-using" should read --Condoms Using--;

Column 1, line 62 "device This" should read --device. This-  
- to correspond with page 3, line 7 of the application;

Column 3, line 41 "virus" should read --virus,-- to correspond with page 7, line 23 of the application;

Column 4, line 62 "elastic" should read --elastic-- to correspond with page 11, line 17 of the application; and

Column 6, line 27 "rounded At" should read --rounded. At-- to correspond with page 15, line 24 of the application.

The errors in the issued patent also include mistakes of a clerical or typographical nature, or of minor nature, which are not the fault of the U.S. Patent and Trademark Office and occurred in good faith. Correction of these mistakes does not involve such changes in the patent as would constitute new matter or would require re-examination. The mistakes which are not the fault of the U.S. Patent and Trademark Office are listed below:

At page 25, line 5 of the application and in the Abstract, line 4 of the patent "end" should read --end having--;

At page 3, line 5 of the application and at column 1, line 60 of the patent "are" should read --is--;

At page 3, line 18 of the application and at column 2, line 5 of the patent "useful" should read --not useful--;

At page 5, line 5 of the application and at column 2, line 42 of the patent "thin-walled," should read --thin-walled--;

At page 6, line 2 of the application and at column 2, line 61 of the patent "condom like" should read --condom-like--;

At page 10, line 1 of the application and at column 4, line 22 of the patent "is" should read --are--;

At page 14, line 6 of the application and at column 5, line 55 of the patent "a insertion" should read --an insertion--;

At page 14, line 10 of the application and at column 5, line 59 of the patent "inserted" should read --insertion--;

At page 16, line 13 of the application and at column 6, line 41 of the patent "2" should read --2 of-- and "1" should read --1,--;


At page 17, line 20 of the application and at column 7, line 6 of the patent "that" should read --than--;

At page 18, line 4 of the application and at column 7, line 15 of the patent "internal of" should read --internal or--; and

At page 18, line 6 of the application and at column 7, line 17 of the patent "attatched" should read --attached--.

Enclosed is a check in the amount of \$70.00 in payment of the fee for correction of applicants mistake. Also enclosed is a check in the amount of \$4.50 in payment of the fee for 15 additional copies of the certificate of correction. Please charge or credit Deposit Account Number 12-1210 if the amount of either check is incorrect.

June 1, 1992  
Date

  
\_\_\_\_\_  
Karen Lee Orzechowski  
Reg. No. 31,621  
Attorney for Applicant

LEVY, ZITO & GRANDINETTI  
Suite 411  
1910 K Street, N.W.  
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(202) 429-4560

# UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 4,976,273

DATED : December 11, 1990

INVENTOR(S) : HESSEL, Lasse

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Related U.S. Application Data, line 1, "Jun. 15, 1987" should read --Jun. 5, 1987--

In the Other Publications, line 4, "1934," should read --1934),--

In the Other Publications, line 7, "condoms-using" should read --Condoms Using--

In the Abstract, line 4, "end" should read --end having--

Column 1, line 60 "are" should read --is--

Column 1, line 62 "device This" should read --device. This--

Column 2, line 5 "useful" should read --not useful--

Column 2, line 42 "thin-walled," should read --thin-walled--

Column 2, line 61 "condom like" should read --condom-like--

Column 3, line 41 "virus" should read --virus,--

Column 4, line 22, "is" should read --are--

Column 4, line 62 "elastic" should read --elastic--

Column 5, line 55, "a insertion--" should read --an insertion--

Column 5, line 59, "inserted" should read --insertion--

Column 6, line 27 "rounded At" should read --rounded. At--

Column 6, line 41, "2" should read --2 of-- and "1" should read --1,--

Column 7, line 6, "that" should read --than--

Column 7, line 15, "internal of" should read --internal or--

Column 7, line 17, attached" should read --attached--

MAILING ADDRESS OF SENDER

Levy, Zito & Grandinetti  
1910 K Street, N.W., Suite 411  
Washington, D.C. 20006-1104

PATENT NO. 4,976,273

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : HESSEL, Lasse  
Serial Number : 148,992 Examiner: Pellegrino, S.  
Art Unit: 336  
Filed : January 27, 1988  
For : TUBULAR PROTECTIVE DEVICE FOR  
PROTECTION AGAINST TRANSFER OF  
INFECTIOUS MATTER DURING SEXUAL  
INTERCOURSE

TERMINAL DISCLAIMER

Honorable Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Sir:

The undersigned petitioner represents that Chartex International Plc, a corporation of England and Wales, is the owner of the entire right and interest of U.S. Patent No. 4,735,621 and the entire right and interest of the above-identified application and that he is an officer of said corporation duly authorized to make this Terminal Disclaimer, said petitioner hereby disclaims, under 35 U.S.C. 253, the terminal part of any patent granted on said application which would extend beyond the expiration date of U.S. Patent No. 4,735,621 and hereby agrees that any patent so granted on the above-identified application shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to United States Patent No. 4,735,621, this agreement to run with any patent granted on the above-identified application and to be binding upon the grantee, its successors or assigns.

9 MAY 1990  
Date

KARL KRISTIAN JENSEN  
Signature

KARL KRISTIAN JENSEN  
Name

MARKETING DIRECTOR  
Title

E

APPENDIX E-SUMMARY OF SIGNIFICANT ACTIVITIES

1987

Clinical research of FEMSHIELD (predecessor to REALITY/FEMIDOM) initiated in the U.K.

1988

January 27, 1988      Application for U.S. Patent No. 4,976,273 was filed.

April 5, 1988        U.S. Patent No. 4,735,621 issued.

April 8, 1988        Clinical research and development of the WPC-333 in U.S. initiated, human research underway prior to patent issue date becomes claimable to establish regulatory period under 37 C.F.R. §1.777.

May, 1988            WPC-333 clinical studies were initiated as a Class II device.

December, 1988      Initiated long-term shelf-life study.

1989

March, 1989          FDA OB-GYN Advisory Panel recommended vaginal pouches classified as Class III.

August, 1989        Second FDA OB-GYN Advisory Panel meeting recommended that vaginal pouches classified as Class III.

October, 1989        Formal guidelines recommended by FDA Advisory Panel for Class III evaluation of vaginal pouches.

1990

April 3, 1990        Use-Effectiveness study initiated.

August, 1990        Initiated study of long-term storage in a foil/paper laminate heat sealable pouch of silicone-lubricated devices.

December 11, 1990      U.S. Patent No. 4,976,273 issued.

1991

February, 1991      Completed long-term shelf-life study.

April 3, 1991        WPC letter to FDA's Dr. R. Kammula regarding interim results.

APPENDIX E  
Page 2

July, 1991	Initiated study to assess the effect of high humidity conditions on the stability of the vaginal pouch.
July 15, 1991	Fully audited data collected as of this date with 63 women completing six months of use (reported 10/29/91 PMA).
July 24, 1991	Initiated tissue culture cytotoxicity test for device.
August 8, 1991	Completed tissue culture cytotoxicity test for device.
September 1, 1991	Unaudited results with 114 women completing six months of use (reported 10/29/91 PMA).
September 30, 1991	WPC initiated sensitization assay on lubricated devices.
October 9, 1991	Initiated Vaginal Irritancy Study-Rabbits.
October 9, 1991	BF Goodrich letter to FDA permits WPC to refer to DMF-5361 in FDA's evaluation of WPC device.
October 24, 1991	Initiated acute vaginal irritation study.
October 29, 1991	Initiated study of long-term vaginal irritation for device.
<u>October 29, 1991</u>	PMA P910064 filed (master file 292) included an interim report on the Pregnancy Use-Effectiveness.
November 7, 1991	Completed acute vaginal irritation study.
December, 1991	Summary of Interim Findings for Use-Effectiveness.
December 6, 1991	Completed study of long-term vaginal irritation for device.
December 17, 1991	Amendment #1 to PMA.
December 18, 1991	FDA sent letter with questions to WPC.
December 19, 1991	Amendment #2 to PMA.

APPENDIX E  
Page 3

December 27, 1991      Parts I & II Use-Effectiveness Database  
Update PMA-P910064 Sup001 completed.

December 30, 1991      Completed report of study of long-term  
storage in a foil/paper laminate heat  
sealable pouch of silicone-lubricated  
devices.

December 30, 1991      Amendment #3 to PMA.

1992

January 3, 1992      Completed study for sensitization assay of  
lubricated devices.

January 7, 1992      Received letter from BF Goodrich regarding  
gel permeation chromatography determinations  
of the molecular weights for the aged "dry"  
and wet Estane (brand) thermoplastic  
polyurethane used to manufacture the vaginal  
pouch.

January 8, 1992      Sup002 FDA questions WPC responses.

January 9, 1992      Amendment #4 to PMA.

January 15, 1992      Amendment #5 to PMA.

January 23, 1992      Initiated bacteriophage stability study in  
Tween (Polyoxyethylene-20-Sorbitan  
MonoOleate).

January 25, 1992      Completed bacteriophage stability study in  
Tween(Polyoxyethylene-20-Sorbitan  
MonoOleate).

January 30, 1992      Amendment #6 to PMA.

January 31, 1992      FDA requested rip/tear study.

January 31, 1992      WPC presentation to FDA OB-GYN Devices Panel.

February 26, 1992      Amendment #7 to PMA--WPC submission of  
rip/tear study.

March 26, 1992      FDA requests responses from WPC.

April 13, 1992      Amendment #8 to PMA.

APPENDIX E  
Page 4

April 15, 1992	Amendment #9 to PMA.
April 30, 1992	WPC sent responses to FDA including Post-Coital Leak Test.
June 10, 1992	Completed Vaginal Irritancy Study-Rabbits.
June 24, 1992	Amendment #10 to PMA.
July 16, 1992	Amendment #11 to PMA.
July 30, 1992	WPC answers to FDA questions.
July 30, 1992	WPC Responses to FDA Questions of March, 1992.
July 31, 1992	Amendment #12 to PMA.
August 3, 1992	Amendment #13 to PMA.
September 28, 1992	Amendment #14 to PMA.
October, 1992	FDA presented questions to WPC.
October 30, 1992	Amendment #15 to PMA.
November 13, 1992	WPC sent responses to FDA questions related to Contraceptive Efficacy Study for the device.
November 16, 1992	Amendment #16 to PMA.
December 1, 1992	WPC provides responses to FDA questions.
December 1, 1992	Amendment #17 to PMA.
December 4, 1992	Amendment #18 to PMA.
December 7, 1992	Amendment #19 to PMA.
December 10, 1992	WPC presentation to 49th Meeting of OB-GYN Panel.
December 16, 1992	Amendment #20 to PMA.
December 18, 1992	Amendment #21 to PMA.

APPENDIX E  
Page 5

1993

January 22, 1993	Amendment #22 to PMA.
January 29, 1993	Amendment #23 to PMA.
February 2, 1993	Amendment #24 to PMA.
February 9, 1993	Amendment #25 to PMA.
March 4, 1993	Amendment #26 to PMA.
April 16, 1993	Amendment #27 to PMA.
April 26, 1993	FDA letter to WPC designating device as "approvable".
May 7, 1993	FDA letter to WPC designating device as "approved". Appendix B.

## CLINICAL TRIAL and SURVEY REPORT

Report no. 007 APRIL 1993

NO.	STUDY NAME	SPONSOR	INVESTIGATOR /SITE	COMPLETE DATE	EVALUABLE PT NO.	NO OF USES	REPORT RECEIVED	STATUS
1	Re-infection	WPC	Shangold, Chicago	Sep-90	54	approx 1K	Oct-90	Poster presentation. Accepted for publication - STD
2	Vaginal Trauma	WPC	Soper, VA	Feb-91	15	90	Feb-91	Published. Contraception Vol 44, No. 1
3	Use Effectiveness	USAID	FHI/Conrad	Mar-92	359		Jul-92	Awaiting publication
4	Permeability Study	WPC	Voeller, Mariposa	Apr-91	Nil	Nil	May-91	Published. JAMA 266:21
5	Dynamic Study	Chartex	Lees, Middlesex		9	16	Oct-91	Presented. To be submitted to B.J. of Family Planning
6	Allergy Study	Chartex	Forsyth, Glasgow	Apr-91	120	Nil	Nov-91	Presented. To be published
7	Long Term Behaviour	Chartex	Nick Ford, Exeter	Feb-92	179	1705	Apr-92	Reports available. To be published in July BJFP.
8	Dyspareunia Study	Chartex	Dr A Riley, Bolton	May-91	16	78	Jul-91	Presented. To be submitted to Journal of Sexual Health
9	Acceptability Study	Chartex	Rutgers, Netherlands	Jun-91	166	468	Aug-91	To be published
10	Acceptability	Chartex	Leningrad	Feb-91	100	2400	May-91	Phase II on hold
11	Acceptability Study	FHI	Tansathit, Thailand	Mar-90	12	155	Nov-91	Published
12	Permeability Study	Chartex	Pasteur Institute	Mar-92			May-92	Complete.
13	Acceptability Study	Chartex	Hoffman, Karlsruhe	Sep-91	(37)	(185)		Interim results presented. Awaiting final report.
14	Acceptability Study	Chartex	Nadal Mur, Madrid	Apr-91	20	100	1991	Complete
15	Acceptability Study	Rhone Poulenc	Dr H Lehto, Helsinki	Mar-91	49	490		Complete
16	Male Acceptability	WPC	Howard Brown Clinic		11	31		Complete
17	Instruction Leaflet	WPC	Shangold, Chicago		10	10		Complete
18	Acceptability. Phase 1	FHI	Nairobi O&G, Kenya		38	68	Mar-91	Complete
19	Phase II Acceptability. Phase 1 Phase II	FHI	Cameroon		12	45		
					38	1 c1367	Oct-91	Complete
					34			
20	Post-coital leak	WPC	IBRD, Irvine, USA		108	521		Published. Advances in Contraception 5, 229-235 & AIDS Care Vol 2, No. 3.
21	Functional Risk	WPC	Research Testing Lab USA	Nov-88	49	147		"

( ) denote estimated dates or figures

F

NO.	STUDY NAME	SPONSOR	INVESTIGATOR/ SITE	COMPLETE DATE	EVALUABLE PT NO.	NO OF USES	REPORT RECEIVED	STATUS
22	Functional Risk/ Acceptability	WPC	Research Testing Labs, USA		49	294		"
23	Post-Coital Sperm	WPC	Shangold, Chicago		15	76		"
24	Acceptability Study,	Chartex	Guillebaud	1988	24	147		Published. BJ of Family Planning 14, 83-87
25	Acceptability Study	FHI	Sakondhavat, Thailand	Feb-91	20	78	Apr-91	Presented & published AJPH Apr '90, Vol 80. No 4
26	Acceptability Study	FHI	Sakondhavat, Thailand		86	c400	Feb-91	Preliminary report.
27	Permeability Study	WPC	Drew, California		Nil	Nil		Published. Sexually Transmitted Diseases 17
28	Acceptability survey in drug users	WPC	Schilling, N.Y.		57	0		Poster presented & published
29	Acceptability	Polivé	De Vincenzi, Paris	Jan-92	27	116	Feb-92	AlPH, Oct '91, Vol 81 No.10
30	Use-effectiveness	WPC/Chartex	Bounds, London		106	unknown	Jan-92	Poster presentation, AIDS World Congress. For publication
31	Acceptability Survey	Chartex	Germany	1988	206	1030		Published. Br.J.Fam.Plann., 1992;18:36-41
32	Acceptability Study	Polivé	Henrion, France	Jan-92	45	c125		Completed
33	Acceptability	Polivé	Mimoun		(80)	(480-800)		Presented May 92
34	Acceptability (Cultural comparison)	Polivé	Janse-Marec		(40)	(200)		To start March 92.
35	Acceptability	Ferrosan	Denmark	Oct-92	70	269	(Feb-93)	Completed. No report expected.
36	Post-coital dysuria	Chartex	Riley, UK	(Oct-92)	(40) (Interim analysis @ 20)	(40)		Written report still awaited
37	15cm vs. 17cm device	FHI	Bennett, Thailand	Mar-92	10	131	Apr-92	Underway
38	Acceptability in post partum women	Polivé	Janse-Marec, France		(50)	(250)		Completed
39	Post-coital leak	WPC	R T Labs, USA	Jun-92	50	238		Underway
40	Reinfection	Chartex	D Hicks, UK					Completed
41	Use Acceptability	WHO	DCDC, Thailand	Jun-93	(300)			Postponed indefinitely
42	Acceptability	Chartex	Sapire, South Africa	(Aug-93)	(100)	(1000)		Protocol agreed. Yet to start
43	Acceptability	Salus Brauma-	Leodolter, Austria	(Oct-92)	20	120		?Started end March
								Complete. Press release issued

( ) denote estimated dates or figures

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM

<u>Studies</u>	<u>IDE</u>	<u>No of Centers</u>	<u>No of Subjects Using WPC-333</u>	<u>No of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
<u>A. Wisconsin Pharmaceutical Sponsored Studies</u>							
1. Post-Coital Leak	NR*	10	108	521	Institute for Biological Research and Development, Inc. (IBRD)	Comparative study with male condom. Examine each used device for leaks and tears using ASTM water-leak test.  Results:  WPC-333      0.6% leakage rate Male Condom      3.5% leakage rate	A, IV-2
2. Functionality/ Dislodgement	NR*	1	49	147	Research Testing Laboratory	Comparative study with male condom. Determine risk of vaginal exposure to seminal fluid due to dislodgement and tears during use.  Results:  WPC-333      2.7% exposure risk Male Condom      8.1% exposure risk	A, IV-3

• NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.

• Estimated

• At completion

• Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No of Centers</u>	<u>No of Subjects Using WPC-333</u>	<u>No of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
3. Functionality/ Dislodgement	NR*	1	49	294	Research Testing Laboratory	Comparative study using two different lubricating systems - silicone and water-based containing spermicide. Determine risk of vaginal exposure to seminal fluid due to dislodgement and tears.	A, IV-4
						Results:	
						No statistical difference between the two lubricants.	
						WPC-333 2.05% exposure risk	
4. Post-Coital Sperm Deposition	NR*	1	15	76	Shangold, G; University of Chicago	Examine vagina for seminal fluid following use of WPC-333 during intercourse. No sperm were observed or detected.	A, IV-5
						Results:	
						WPC-333 0% sperm observed	

. NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.  
 .. Estimated  
 ... At completion  
 .... Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No of Centers</u>	<u>No of Subjects Using WPC-333</u>	<u>No of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
5. Reinfection Rate	NR* G900114	6	53	1,000**	Shangold, G; University of Chicago	Determine reinfection rate of trichomonas and/or chlamydia in high-risk women when WPC-333 is used every time during sexual intercourse over 45 days.	A, IV-9
Results:							
Compliant Users      0% reinfection							
Non-Compliant Users      14.7% reinfection							
Controls      14% reinfection							
6. Vaginal Trauma	Yes G890229	1	15	120**	Soper, D; Medical College of Virginia	Examine vagina and lower genital tract for any changes to vaginal flora, trauma, irritations, including colposcopic examination following repeated and prolonged use of WPC-333 or diaphragm.	A, IV-6
Results:							
No significant changes or trauma noted when WPC-333 was used.							

• N/R - not required: Study initiated prior to Guidelines or ex-U.S. study sponsored by Chantex International.

•• Estimated

••• At completion

•••• Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No. of Centers</u>	<u>No. of Subjects Using WPC-333</u>	<u>No. of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
7. Use Effectiveness	Yes G890203	9	200*** 270****	20,000*** 12,000****	Rivera, R; Family Health International (FHI)/ Contraceptive Research & Development Program (CONRAD)	Six months use; pregnancy rate.  Results:  Life-Table Analysis:  U.S. 3 mo. Ex-U.S. 3 mo. All 3 mo. 7.54	A, IV-8
8. Instruction	Yes G900001	1	10	30	Shangold, G; University of Chicago	Determine if instructions for use are clear and understood by women with low level of education.  Results:  All of the women inserted WPC-333 correctly, had no questions regarding insertion, nor did they suggest any changes to the instructions.	A, IV-7

• NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.

• Estimated

• At completion

• Estimated, 9/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No of Centers</u>	<u>No of Subjects Using WPC-333</u>	<u>No of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
9. Acceptability in Anal Intercourse	Yes G900066	1	14	31	Jobst, R; Howard Brown Memorial Clinic	Determine rips and tears following use in anal intercourse by gay men.  Results:  There were no rips or tears.	A, IV-11
<b>B. <u>Ex-U.S. Studies</u></b>							
1. Dynamic - UK	NR*	1	10	20	Lees, W; Middlesex Hospital London	Observe the physical dynamics and stability of using <i>Femidom</i> ™ (a) during intercourse, particularly the inner ring, using ultrasonography.  Results:  Device was highly stable throughout intercourse.	A, IV-12

NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.

.. Estimated

... At completion

.... Estimated, 7/91; study ongoing

(a) European tradename for WPC-333

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No. of Centers</u>	<u>No. of Subjects Using WPC-333</u>	<u>No. of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
2. Allergy - UK	NR*	1	150	patches	Forsyth, A; Belvedere Hospital Glasgow	Evaluate potential for allergic response of using polyurethane device in latex-sensitive individuals.  Results:  No significant reactions to any part of the device or lubrication.	A, IV-13
3. Acceptability - Thailand							
a.	NR*	3	86	400**	Bennett, T; Family Health International (FHI)	Evaluate acceptability by prostitutes operating in different cities.  Results:  Use was related to education level, client response, and fear of AIDS. Average use was 10%. Author recommended distribution through Ministry of Public Health.	A, IV-14

• NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.  
 • Estimated  
 •• At completion  
 ••• Estimated, 7/91; study ongoing  
 ••••

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No of Centers</u>	<u>No of Subjects Using WPC-333</u>	<u>No of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
3b.	NR*	2	40	210	Chunchoom; F a m i l y   H e a l t h International (FHI)	Evaluate acceptability of a female barrier device by prostitutes - 2 studies.  Results:  Preliminary research indicates that prostitutes will use female condom.  Study 1 - Device used in approximately 30% of episodes.  Study 2 - Device used in approximately 20% of episodes.	A, IV-14

• NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.

• Estimated

• At completion

• Estimated, 7/91: study ongoing

••••

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No. of Subjects Using WPC-333</u>	<u>No. of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
3c.	NR*	14	70	Transathit, T; Chiang Wai University WHO sponsored	Pilot study to evaluate acceptability by Thai women.  Results:  Generally accepted; 58% women would use in future. Particularly positive for STD use.	A, IV-14
4. Acceptability - Netherlands	NR*	3	166	500  Rutgers Stichting	Determine overall acceptability in general population of sexually active women.  Results:  8% said they would certainly use; 22% said maybe would use. Most women and men felt that it provided good protection against pregnancy and AIDS.	A, IV-15

. NR - not required. Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.  
 .. Estimated  
 ... At completion  
 .... Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No. of Centers</u>	<u>No. of Subjects Using WPC-333</u>	<u>No. of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
5. Acceptability USSR	NR*	1	100	2,500	Ailamazyan, University of Leningrad	Evaluate acceptability over 3 months use.  Results: 97% were satisfied. No pregnancy was recorded.	A, IV-16
6. Acceptability Kenya	NR*	3	38	113	Ruminjo; Kenyatta Hospital Family Health International (FHI)	Evaluate acceptability compared to male condom in low-risk women.  Results: 84% were positive to device. 39% preferred the female condom; 37% liked it just as well as a male condom.	A, IV-17

• NR - not required. Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.

• Estimated

• At completion

• Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No of Centers</u>	<u>No of Subjects Using WPC-333</u>	<u>No of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
7. Acceptability - Cameroon	NR*	1	38	1,800	Monny Lobe, M; Blood Bank at Central Hospital	Assess acceptability in a population of high-risk women.  Results:  WPC-333 found to be very acceptable.  61% liked it very much 34% like it fairly well	A, IV-18
8. Dyspareunia - UK	NR*	1	15	75	Riley, A; ACR, Bolton	Assess the tolerance of the device in menopausal women complaining of dyspareunia.  Results:  Device well tolerated; appeared to reduce pain associated with penile penetration.	A, IV-19

• NR - not required. Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.

• Estimated

• At completion

• Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No. of Centers</u>	<u>No. of Subjects Using WPC-333</u>	<u>No. of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
9. Acceptability - U.K.	NR*	1	134	4,147**	Guillebaud, J; Margaret Pyke Center (MPC)	Two studies: General acceptability and a use-effectiveness study.  The first study was an early study on the WPC-333 prototype (different length). The results were positive.  The use-effectiveness study was discontinued before completion. MPC experienced a large drop-out rate (76%).	
10. Acceptability - Germany	NR*	2	27	110	Hoffman, K; Karlsruhe and Hamburg, Institute für Familienplanung	Evaluate acceptability compared to male condom.  Results:  In process.	

\* NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Charlex International.

\*\* Estimated

... At completion

.... Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

<u>Studies</u>	<u>IDE</u>	<u>No. of Centers</u>	<u>No. of Subjects Using WPC-333</u>	<u>No. of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
11. Acceptability - Spain	NR*	5	40	100	Mur, N.F. Clinica Belen, Madrid	Evaluate acceptability.  Results:  85% of couples found <i>Femidom</i> acceptable.	A, IV-21
12. Acceptability - Finland	NR*	3	98	490	Lehto, H. Helsinki City Contraceptives Clinics	Evaluate acceptability; compared to male condom.  Results:  59% found <i>Femidom</i> acceptable. 25% preferred <i>Femidom</i> to male condom.	A, IV-22

• NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.  
 • Estimated  
 • At completion  
 • Estimated, 7/91; study ongoing

SUMMARY OF CLINICAL STUDIES - WORLDWIDE USING WPC-333/FEMIDOM (Cont'd.)

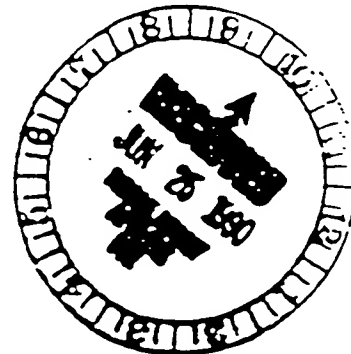
<u>Studies</u>	<u>IDE</u>	<u>No of Centers</u>	<u>No of Subjects Using WPC-333</u>	<u>No of Uses of WPC-333</u>	<u>Principal Investigator/ Institution</u>	<u>Comments including: Objective and Results</u>	<u>Location in PMA</u>
13. Long-Term Behavior - UK	NR*	20	123 250***	400 7,000***	Philips, D; Institute of Population Studies University of Exeter	Determine behavioral requirements of acceptance and comparative acceptability versus male condom.  Results:  In process. Preliminary information in report.	A, IV-20
14. Acceptability - France	NR*	1	30	150	Brunet, J-B. Centre European Pour La Surveillance Epidemiologique du Sida, WHO	Evaluate acceptability of <i>Femidom</i> in prostitutes.  Results:  In process.	A, IV-23

\* NR - not required: Study initiated prior to FDA Guidelines or ex-U.S. study sponsored by Chartex International.  
 .. Estimated  
 ... At completion  
 .... Estimated, 7/91; study ongoing

JUN 20 1990

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

William L. Hunt, Ph.D.  
Director  
Regulatory Affairs  
Family Health International  
P.O. Box 13950  
Research Triangle Park, North Carolina 27709



Re: G890203/S3  
Reality<sup>TM</sup> Intravaginal Pouch (WPC-333)  
Dated: May 16, 1990  
Received: May 21, 1990

Dear Dr. Hunt:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing to revise the Physician's Brochure, "Checklist for Client Recruitment" to require complete informed consent process prior to a subject's initial insertion of the device in the clinic. Your supplement is approved, and you may implement that change at the institutions previously enrolled in your investigation.

We would like to point out that FDA approval of your supplement does not imply that this investigation will develop sufficient safety and effectiveness data to assure a determination of substantial equivalence of a premarket notification (510(k)) submission or sufficient safety or effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers Assistance at their toll free number (800) 638-2041 or (301) 443-6597.

If you have any questions, please contact Raju G. Kammila, D.V.M., Ph.D. at (301) 427-1180 or Nancy F. Teague, M.P.H. at (301) 427-1190.

Sincerely yours,

*Lillian Yin*  
for Lillian Yin, Ph.D.  
Director, Division of Ob-Gyn,  
ENT and Dental Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

## MASTER AGREEMENT

This Master Agreement is made between the Institute for Biological Research & Development, Inc., a Delaware Corporation ("IBRD"), and Wisconsin Pharmacal Company, a Wisconsin Corporation ("Sponsor").

WHEREAS, Sponsor requires the conduct of a clinical trial study to determine the user-acceptability and assessment of structural integrity of WPC-333, a female condom ("WPC-333"), and the completion of a final clinical trial report appropriate for submission to the United States Food and Drug Administration ("FDA"); and

WHEREAS, IBRD has broad experience in clinical trial management, clinical data collection systems, and preparation of clinical trial data bases appropriate for submission to the FDA or other governmental agencies;

IBRD and the Sponsor agree to the following:

### SECTION 1

#### IBRD SUPPORT STAFF

1.1 IBRD will appoint a project director and support staff for the enrollment of clinical trial investigators, monitoring the clinical trial, review and analysis of data obtained from the clinical trial, and such other activities as may be necessary for the completion of a final clinical trial study report for the evaluation of WPC-333 according to Protocol A (Attachment I and incorporated by reference to


**PAGES TWO THROUGH TWENTY-ONE OF THE MASTER AGREEMENT  
CONTAIN BUSINESS SENSITIVE INFORMATION.**

**PAGES ONE AND TWENTY-TWO OF THE MASTER AGREEMENT  
ARE PROVIDED TO ESTABLISH FDA-RELATED ACTIVITIES IN 1988.**

IN WITNESS WHEREOF, the undersigned have executed this Master Agreement as of the day and year written below.


IBRD:

INSTITUTE FOR BIOLOGICAL RESEARCH  
AND DEVELOPMENT, INC.

  
\_\_\_\_\_  
Pamela J. Kane  
Vice President of Finance  
and Administration

4-8-88  
Date

SPONSOR:

  
\_\_\_\_\_

4-14-88  
Date

Exec. V. Pres.  
\_\_\_\_\_  
Title

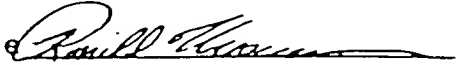
INSTITUTE FOR BIOLOGICAL RESEARCH AND DEVELOPMENT, INC.

INSTITUTIONAL REVIEW BOARD

SPONSOR DISPOSITION MEMORANDUM

To: Wisconsin Pharmacal Company  
2977 Highway 60  
P.O. Box 198  
Jackson, Wisconsin 53037

From: Ronald L. Thommarson, M.D.  
Chairman,  
Institutional Review Board

Signature 

Protocol: A

IRB No.: HS-88-02  
Project No.: PHOEN8701

Protocol Title: A STUDY OF THE USER-ACCEPTABILITY OF WPC-333, A NEW FEMALE BARRIER FOR SEXUALLY-TRANSMITTED DISEASES AND CONTRACEPTION, COMPARED TO A STANDARD MALE CONDOM

APPROVAL DATE: MAY 16, 1988

The protocol referenced above dated April 11, 1988 and the Informed Consents (one for female and one for male participants) were reviewed and approved by the Institutional Review Board on April 19, 1988. Protocol Addendum No. 1 dated May 13, 1988 and the revised Informed Consents were reviewed and approved on May 16, 1988.

The Informed Consents dated May 16, 1988 must be used without alteration. All patients/participants must sign the appropriate Informed Consent and the Investigational Subject's Bill of Rights and be given a copy of each to take home. No changes should be made in the above referenced protocol without prior approval by the Institutional Review Board.

The Board requires as a condition of its approval that it receive follow-up reports from each investigator every 12 months and /or when the study is completed; which shall include the number of subjects who have participated and any untoward or unexpected reactions on the part of these subjects. A form requesting the appropriate information regarding the status of the project will be sent to the investigators prior to the follow-up review date.

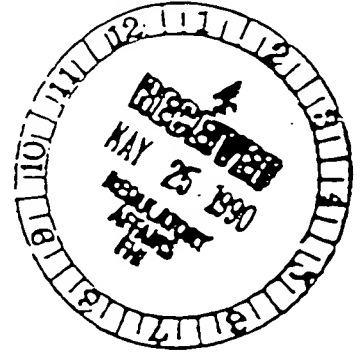
The Board requires that the investigators report to it and to Wisconsin Pharmacal Company within 48 hours of awareness, any unanticipated adverse effects or the death of any patient. The Board may be notified through the Institute for Biological Research and Development, Inc. at (714) 476-2727. The investigators are also instructed to document their contact to the Sponsor and to the Board on the patient's case report form.

cc: IBRD

MAY 22 1990

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

William L. Hunt, Ph.D.  
Director  
Regulatory Affairs Division  
Family Health International  
P.O. Box 13950  
Research Triangle Park, North Carolina 27709



Re: G890203/S2  
Reality<sup>TM</sup> - Intravaginal Pouch (WPC-333): Phase II Clinical Study  
Dated: April 25, 1990  
Received: May 1, 1990

Dear Dr. Hunt:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing the addition of two additional institutions to increase the number of sites from 7 to 9. Your supplement is approved and you may begin your investigation at the institutions after you have obtained institutional review board (IRB) approval. Your investigation is limited to nine institutions and 300 subjects. FDA acknowledges that 3 institutions have received IRB approval and include:

Eastern Virginia Medical School  
Norfolk, Virginia

University of Arizona  
Tucson, Arizona

Valley Center for Women's Health  
Sacramento, California

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of IRB approval for the addition of investigation sites (21 CFR 812.35(d)) provided:

1. The total number of investigation sites does not exceed 9.
2. You maintain current records on:
  - a. the names and addresses of all investigational sites,
  - b. the names and addresses of all investigators, and identifying those that are currently participating,
  - c. the names, addresses and chairperson of all IRBs,
  - d. the dates of IRB approvals, and
  - e. the dates of first shipments or first use of investigational devices for all participating institutions.
3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.
5. You submit to FDA, within 2 days of receipt of a request by FDA a current list containing the information specified in 2(a-e) above.
6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has improved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. You must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation past the limit specified above. If you do not agree to these conditions, you must comply with the full requirements of submission of a supplemental IDE application for new investigational site (21 CFR 812.35(b)). FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement.

FDA has also reviewed your proposed changes in the investigational plan and informed consent document. Your request for changes in the investigational plan, identified as 1, 2, and 4 - 8 and the changes in the informed consent document (reference: Proposal 958 - Amendment 1, three pages) are approved, and you may implement those changes at the institutions identified above and at new institutions that meet the requirements above.

We regret to inform you that your request to amend exclusion criterion number 10 with the addition of the sentence, "Volunteers with Pap smears that have cellular changes associated with HPV but do not indicate dysplasia may be admitted into the study," (proposed change number 3) is disapproved and you may not implement this change in your investigational plan. Our disapproval is based on the Human Papilloma Virus (HPV) being a sexually transmitted disease (STD) which presents significant risk to the study subjects and that its presumed presence, suspected by "cellular changes associated with HPV" may either mask a change in a subject's Pap smear due to the device or may exacerbate a change in a subject's Pap smear. If you submit information justifying the addition of this as an exclusion (inclusion) criterion, FDA will reevaluate this proposed change in the investigational plan. This information should be identified as an IDE supplement referencing the IDE number, and must be submitted in triplicate to:

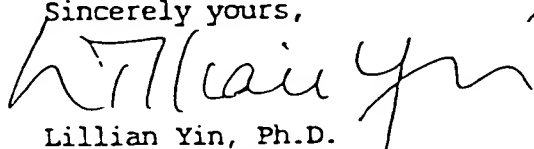
IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Page 3 - William L. Hunt, Ph.D.

We must inform you that you have an opportunity to request a regulatory hearing regarding our disapproval of your IDE supplement. Procedures governing any such hearing are described in the enclosure "Procedures to Request a Regulatory Hearing."

If you have any questions, please contact Raju G. Kammula, D.V.M., Ph.D., at (301) 427-1180 or Nancy F. Teague at (301) 427-1190.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Lillian Yin".

Lillian Yin, Ph.D.  
Director, Division of OB/GYN, ENT  
and Dental Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

Enclosure

PROCEDURES TO REQUEST A REGULATORY HEARING

In order to request a regulatory hearing regarding FDA's disapproval or proposed withdrawal of approval of your IDE application, you are required to file the request within 30 days from the date of FDA's letter stating such decision. If FDA has not received from you a request for a hearing within that time, you will be considered to have foregone the opportunity to request a hearing and no hearing will be held. Any request for a hearing may be filed by mail, telegram, telex, personal delivery, or any other written mode of communication, and addressed to the following person:

Warren Howard  
Division of Regulations Policy (HFC-220)  
Office of Regulatory Affairs  
Food and Drug Administration  
5600 Fishers Lane, Room 12A-17  
Rockville, MD 20857  
(301) 443-3480

This notice of an opportunity for a regulatory hearing and any hearing on FDA's disapproval or proposed withdrawal of approval of the IDE application is governed by 21 CFR, Part 16, and section 201(y) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(y)).

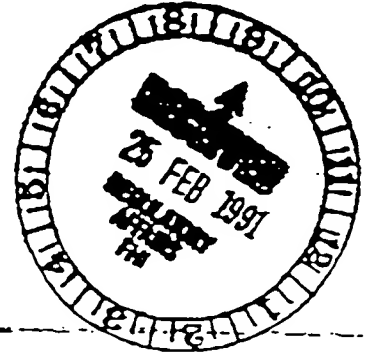
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

FEB 20 1991

William L. Hunt, Ph.D.  
Director, Regulatory Affairs  
Family Health International  
P.O. Box 13950  
Research Triangle Park, North Carolina 27709



Re: G890203/S8  
REALITY™ - Intravaginal Pouch  
Dated: January 16, 1991  
Received: January 23, 1991

Dear Dr. Hunt:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing to change the investigational labeling for the REALITY™ device. Your supplement is approved, and you may implement that change at the institutions previously enrolled in your investigation.

If you have any questions, please contact Raju G. Kammula, D.V.M., Ph.D. at (301) 427-1180 to Nancy F. Teague at (301) 427-1190.

Sincerely yours,

A handwritten signature in cursive script, appearing to read 'Lillian Yin'.

Lillian Yin, Ph.D.  
Director, Division of OB/GYN, ENT,  
and Dental Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

APR - 3 1991

Mary Ann Leeper, Ph.D.  
Director of Development  
Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

Dear Dr. Leeper:

This is in response to your letter of March 7, 1991, regarding the preparation of your premarket approval (PMA) application. In your letter, you requested that I forward information regarding the acceptable use of a historical control group. As I explained during our telephone conversation, when using an historical control group, you must take special precautions to assure that the historical control group and the experimental group have a comparable population profile especially regarding relevant factors. Important relevant factors include age, socioeconomic status, education, parity, previous barrier contraceptive use, etc.

Also, I mentioned during our telephone conversation that the two guidelines, which you had requested in your letter, were already forwarded to you. In the future, you may wish to contact the Division of Small Manufacturers Assistance (DISMA) at (301) 443-6597 or 1-800-638-2041 for available guidelines.

I hope that this information will assist in the preparation of your PMA application. If you have any further questions regarding this matter, please contact me at (301) 427-1180.

Sincerely yours,

Raju G. Kammula, D.V.M., Ph.D.  
Chief, OB/GYN Devices Branch  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

JUN 19 1991

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

Mary Ann Leeper, Ph.D.  
Senior Vice President  
Wisconsin Pharmacal Company, Inc.  
2977 Highway 60  
P.O. Box 198  
Jackson, Wisconsin 53037

Re: MAF-292

Dear Dr. Leeper:

This is to acknowledge receipt of your amendment to the above referenced Master File. This amendment was received by the Center for Devices and Radiological Health on May 10, 1991.

If you require assistance, you may contact the Premarket Approval (PMA) Section at (301) 427-1186.

Sincerely yours,



Mary Jo Robinson  
Assistant to the Director  
Premarket Approval Section  
Center for Devices and  
Radiological Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug  
Center for De  
Radiological  
1390 Piccard  
Rockville, Ma

October 29, 1991

MARY ANN LEEPER  
WISCONSIN PHARMACOL COMPANY  
919 N. MICHIGAN AVENUE  
SUITE 2208  
CHICAGO,, IL 60611

PMA Number: P910064 SUP 000  
Letter Dated: 10/28/91  
Received: 10/29/91  
Product: REALITY(TM) VAGINAL  
POUCH

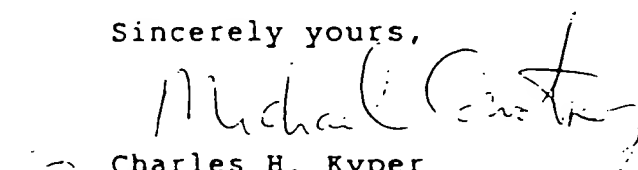
Dear MS. LEEPER:

The Center for Devices and Radiological Health (CDRH) acknowledges its receipt of the premarket approval application (PMA) supplement submitted by you for the above referenced device. This PMA supplement has been assigned an unique document control number. Failure reference this supplement number in further correspondence may result in processing delays. All further correspondence shall be referred to as amendments to the PMA supplement, and the required number of copies bearing the above PMA supplement number shall be submitted directly to:

Food and Drug Administration  
Center for Devices and  
Radiological Health  
PMA Document Mail Center (HFZ-401)  
1390 Piccard Drive  
Rockville, Maryland 20850

You will be notified of any need for additional information and the CDRH filing decision. Questions concerning this submission may be directed to the PMA Staff at (301) 427-1186 or to the reviewing division within the CDRH Office of Device Evaluation.

Sincerely yours,

  
for Charles H. Kyper  
Director, Premarket Approval Staff  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Food and Drug Administration  
1390 Piccard Drive  
Rockville MD 20850

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

DEC - 6 1991

Mary Ann Leeper, Ph.D.  
Wisconsin Pharmacal Company  
919 North Michigan Avenue  
Suite 2208  
Chicago, Illinois 60611

RE: P910064  
Reality™ Vaginal Pouch  
Filed: October 29, 1991

Dear Dr. Leeper:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is October 29, 1991, which is the date of CDRH receipt of the PMA.

CDRH has considered your September 24, 1991, letter requesting expedited review of your PMA. Because the Reality™ Vaginal Pouch is inserted by the woman and because of its potential to prevent the transmission of sexually transmitted diseases (STDs), including the acquired immune deficiency syndrome (AIDS), CDRH will give this PMA expedited processing as described in the reviewer guidance bluebook memorandum #G-89-2 issued by the Office of Device Evaluation (copy enclosed).

This letter reflects the current progress of our review of your application. We will send you a letter shortly that details deficiencies in your application and other safety and effectiveness concerns identified in our review to date. Please be advised that continued review of your application or any response to this letter may result in the identification of additional deficiencies and other review concerns.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update their pending PMA three months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may reasonably affect an evaluation of the safety or effectiveness of the device or may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit update reports in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice regulations (21 CFR Part 820). If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device and provide the expected date that the facility will be prepared for an FDA inspection.

A meeting of the Obstetrics-Gynecology Devices Panel will be held next month at which your PMA will be reviewed. The details are as follows:

Date: Friday, January 31, 1991  
Time: 8:00 a.m.  
Place: Crowne Plaza Holiday Inn  
1750 Rockville Pike  
Rockville, Maryland  
(301) 816-3162

Any update of your clinical study with additional patient data must be received by December 31, 1991, in the form of a PMA amendment. Other additional information to be included in your PMA must be submitted in the form of a PMA amendment and be received by FDA at least 4 weeks (but not less than 3) in advance of the scheduled advisory committee meeting in order for FDA and the panel members to have adequate time to review the new information. Any other additional information received by CDRH less than 3 weeks in advance of a scheduled advisory committee meeting will not be considered or reviewed at the meeting.

For your information, there is an industry representative on this FDA advisory panel whose name, address and telephone number you can obtain by contacting the Committee Management Staff at (301) 443-4016. CDRH believes that the industry representatives will be better prepared to participate in panel discussions if they have been provided with a copy of the Summary of Safety and Effectiveness Data for review prior to the panel meeting. In accordance with 21 CFR 14.86(b), all panel members are subject to all rules and regulations adopted by FDA and the committee; therefore, even though the industry representatives usually are not given access to trade secret and confidential, commercial information, they are bound to protect the confidentiality of documents that would be sent to them in preparation for panel review of a PMA. If you would like the industry representative to have access to any portion of your PMA, including the Summary of Safety and Effectiveness, please provide a copy for that purpose and notify the executive secretary of the panel, Colin Pollard at (301) 427-1194. However, review of your PMA will not be prejudiced if you elect not to provide a Summary for industry representative review.

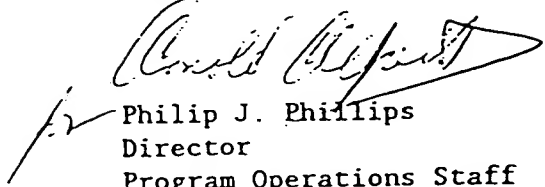
All correspondence regarding this PMA should be submitted in 20 copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Page 3 - Dr. Mary Ann Leeper

If you have any questions, please contact Colin Pollard at (301) 427-1194 or Kathy Lundsten at (301) 427-1186.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Philip J. Phillips", with a large, sweeping flourish extending to the right.

Philip J. Phillips  
Director  
Program Operations Staff  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure



~~November 18, 1991~~

*December 14, 1991*

VIA FEDERAL EXPRESS

Mr. Colin M. Pollard  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Dear Colin:

Re: PMA P910064

Enclosed in this shipment are ten copies of the Reality PMA - each copy is in a separate carton (total ten cartons) and each consists of ten volumes.

This is sent per your request for additional copies to facilitate an expedited review.

We're ready to respond to any questions or requests that FDA may have regarding its review of the PMA - Reality Vaginal Pouch.

Sincerely,

Mary Ann Loeper, Ph.D.  
Director of Development

MAL/dlp

Enclosures:

*10*  
~~Six~~ sets of the ten-volume Reality PMA

My Location:

Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DEC 18 1991

Food and Drug Administration  
1390 Piccard Drive  
Rockville MD 20850

Mary Ann Leeper, Ph.D.  
Wisconsin Pharmacal Company  
919 North, Michigan Avenue  
Suite 2208  
Chicago, Illinois 606114

RE: P910064  
Reality™ Vaginal Pouch  
Filed: October 29, 1991  
Amended: December 17, 1991

Dear Dr. Leeper:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of your premarket approval application (PMA). We regret to inform you that on the basis of this review, we believe that the PMA lacks information needed by CDRH to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use. While the deficiencies outlined below do not preclude further review of your PMA, if left uncorrected, they may ultimately preclude approval.

Although we believe the deficiencies outlined below would normally require the submission of a major amendment, the designation of your PMA as subject to our expedited review procedures has prompted us to administratively handle our concerns as if they were minor deficiencies. This will maintain a continuous 180-day review period and will permit an evaluation of your PMA before the Obstetrics and Gynecology Devices Panel (the Panel) on January 31, 1992.

Neither the length of this letter, nor the number and complexity of the deficiencies outlined below, should be interpreted as a lack of commitment on our part to expeditiously process your application. FDA is committed to improving public health in the area of sexually transmitted diseases (STDs) and doing its part to expeditiously make barrier devices that can be used by women available on the market. Nevertheless, we believe it is just as important that you be fully aware of the safety and effectiveness review concerns that need to be addressed. The fact that we are considering the PMA under our expedited review procedures has prompted us to be as thorough and complete as the timeliness of our response permits. Our goal is to render a decision on your PMA within a 180-day review period.

Our review noted the following deficiencies and, in order to correct these deficiencies, we request the responses as indicated:

Device Materials and Biocompatibility

1. Provide the chemical composition and specifications for both secondary lubricants identified in the PMA (p.305), i.e., the water-based (pf#6003)

2. Provide data from the following biocompatibility tests, conducted on your final lubricated and packaged product, to support its safe use:
  - a. sensitization assay conducted with a nonpolar extract of the device; and
  - b. 90-day muscle implantation test; you must provide gross and histopathological tissue changes, as well as observations on material integrity.
3. Provide quantitative data documenting the detectable levels of methylene dianiline (MDA) in your final product, at the times of manufacture and proposed shelf-life. Also, provide a detailed description of the sample preparation, methodology for detecting MDA, and validation of that methodology.
4. Provide a comprehensive carcinogenicity risk assessment, based upon the detectable levels of MDA in your final product, at the times of manufacture and proposed shelf-life, and the expected device use.

#### Shelf-Life

5. Storage Studies of the Reality™ Vaginal Pouch (Appendix III-1)
  - a. State whether the device samples used in the five storage studies were packaged or unpackaged.
  - b. Provide a full description of the methodology and instrumentation used for control of temperature and relative humidity in the test chambers used to age the specimens in your various storage studies. This must include supporting data.
  - c. Describe the aging process for the devices used in the "Body Fluids Study" (pp.454-464), the "CMC (Water Based) Lubricant Study" (pp.465-469), "Aegis Lubricant (Oil/Water Emulsion) Study" (pp.470-474), and the "CMC Lubricant with Nonoxynol (Water Based With Spermicide) Study" (pp.475-479).
6. 36-month Shelf-Life Data

You provided the gel molecular number of the device material after 12-month aging (p.439-453). Describe the method used to determine gel molecular number, and provide an interpretation of these data.

Provide data from real-time aging studies to demonstrate the chemical stability of the device materials (polyurethane and lubricants) at the proposed 36-month shelf life. This data must include the molecular weight and gel molecular number for the device material at the proposed 36-month shelf life.

#### Barrier (Transport) Studies

7. In general, for each barrier study, you must provide the following:

from proposed clinical use, provide discussion of how this will affect results.

a. Gas Transport Study (pp. 605-634)

- i. The calibration curve for flow (p.609) is not consistent with your stated detection criterion of  $1 \times 10^{-4}$  ml/s (p.611). If a  $\Delta P$  of 0.1 mmHg could actually be measured, then Fig.4.6 (p.609) would give a flow of  $1 \times 10^{-2}$  ml/s, two orders of magnitude larger than the detection criterion. Please clarify.
- ii. Before the helium leakage test can be instituted as an in-process quality assurance method, it must be validated against an established barrier test method for this type of device, possibly the bacteriophage study. See 7(b) and 7(c) below. The validation must be run on whole samples of the device.

b. Dye Studies (pp. 635-671)

- i. Provide a complete drawing (or drawings) of the two-chamber cell, dynamic pressure apparatus used in the dye and bacteriophage studies, as shown in Fig. 6.1, 6.2, and 6.3 (pp.649-651) and Fig. 8.1 (p.673). This drawing (or drawings) should fully illustrate the operation of the diffusion cell. (The photographs provided in the PMA were not useful.)
- ii. What was the "downstream" pressure of the diffusion cell in the dynamic testing? Was it atmospheric pressure, or 8 psig ( $\approx 416$  mmHg), as stated on p.653? How and where were upstream and downstream pressures measured? How is this consistent with the stated maximum pressure drop of 30 mmHg necessary to stay within the elastic limit of the elastomer (p.578)? What happens to the barrier properties when the elastic limit is exceeded?
- iii. What is the sensitivity of this test method? Clearly define what meaningful quantity is used to describe sensitivity.

c. Bacteriophage ( $\phi$ X 174) Study (pp. 672-685)

- i. Again, what is the pressure gradient across the polyurethane pouch and latex condoms used in this study, 30 mmHg or 8 psig? Alternatively, is the pressure gradient at least as great as expected during actual clinical use? If so, provide data documenting these pressures.
- ii. What is the sensitivity of this test method? Again, clearly define what meaningful quantity is used to describe sensitivity. To adequately demonstrate that your device performs as well as latex condoms, data must show that your test method is capable of detecting leakage through holes 5 microns or less. This will

sufficient to "clear" holes this small that may be clogged or sealed?

- iii. Clarify what was the percentage of reduction, or inactivation, of  $\phi$ X 174 that occurred when the virus was exposed to Tween 80 in Dulbecco Solution and distilled water. In the table entitled "Effect of Tween 80 on  $\phi$ X 174 Titre Present in Distilled Water and In Dulbecco Solution" (page 0711), columns 3 and 4 indicate that the virus titer decreased by approximately 80% (i.e., from  $4.6 \times 10^2$  to  $8.5 \times 10^1$ ) while column 5 indicates that there was an 18.5% reduction in virus titer. Provide an explanation for this discrepancy. Also, comment on what effect  $\phi$ X 174 inactivation has on the overall sensitivity and reliability of the test method, and if further inactivation occurs with time.

#### Quality Assurance Control Procedures

8. Provide a detailed description (including diagrams, where appropriate) of both the water leakage test and the in-process (in-line) helium gas leak test, the two tests for establishing the quality of each manufacturing lot. This should include the following:
  - a. a detailed description (including diagrams, where appropriate) of any in-process testing procedures, including a description of the in-process test instrument (with diagrams) and its specifications, a copy of the operator's manual, and a description of the calibration procedures; and
  - b. laboratory data to validate the in-process testing. (See 7(a)(ii) above.) What is the sensitivity of this test method? Again, clearly define what meaningful quantity is used to describe sensitivity.

#### Clinical and Statistical

##### 9. Device Characteristics

Fully characterize the devices used in the clinical studies listed below. Specifically, was a 150mm pouch used in any of the studies? Which secondary lubricant (water-base or oil-base) was provided to subjects in each study?

##### a. Phase I - Feasibility Studies

1. Barrier Design;
2. Post-Coital Leak Test (Study 2);
3. Dislodgement - Two Studies (Studies 3 and 4); and
4. Post-Coital Sperm - Direct Examination (Study 5).

##### b. Phase I - Barrier Safety

1. Vaginal Trauma; and
2. Qualitative Assessment.

c. Instructions for Use Study

d. Phase II: Effectiveness Studies

1. Trichomonas Reinfection Rate; and
2. Pregnancy Use - Effectiveness

10. Phase I - Feasibility Studies

- a. Discuss the bias potential of self-reporting of the spillage of seminal fluid inside the vagina from device slippage and movement, in the Post-Coital Leak Test Study (Study 2) and the Dislodgement Studies (Studies 3 and 4), for estimating vaginal exposure.
- b. Provide a complete description of the method that was used to detect the presence of sperm in the vaginal during the Post-Coital Sperm - Direct Examination Study (Study 5).

11. Phase II: Effectiveness Study - Trichomonas Reinfection Rate

Provide a description of how the compliant and non-compliant groups in the Trichomonas Reinfection Rate Study were defined or determined.

12. Phase II: Effectiveness Study - Pregnancy Use-Effectiveness

- a. Provide a complete description of how the pregnancy rate in the Pregnancy Use-Effectiveness Study was calculated. State whether the pregnancy rate contains only study subjects who completed the study or if it includes study subjects continuing in the study. Provide additional details on how study subjects who discontinued were analyzed.

Compare the results from your Pregnancy Use-Effectiveness Study to those from another historical control study of a barrier contraceptive device that is also used to prevent transmission of sexual transmitted diseases (STDs), i.e., the condom. This is in addition to the other historical control groups which you have chosen.

- b. Provide a monthly lifetable analysis of safety and effectiveness data (i.e., pregnancies rates and discontinuation rates) for the Pregnancy Use Effectiveness Study.

Clearly define discontinuation. Explain the significance of pregnancies in the group of women who discontinued use of the device. Compare the discontinuation rate found in your study to discontinuation rates found in historical control studies of other barrier contraceptive devices.

Explain the relationship between the 16 pregnancies reported in the Phase II Pregnancy Use Effectiveness Study and the 16 pregnancies recorded in the discontinuation rates.

- d. Provide an explanation for the fact that some of the study subjects ineligible for participation in the Pregnancy Use-Effectiveness Study were excluded initially as required by the investigational protocol, while others (with the same exclusion criteria) were included in the group of study subjects who discontinued use of the device.

Device Labeling

13. Patient labeling must include comparative historical control data on other barrier contraceptive devices, including conventional condoms, diaphragms, and cervical caps. Pregnancy and discontinuation rates must be presented in the form of a lifetable analysis.
14. Patient labeling must specify the length of wear during use of an individual device.
15. Provide information on the readability of the English language version of the patient labeling. What grade level education does it require to be properly understood?
16. Provide a copy of the Spanish version of the patient labeling used in the clinical studies (with English translation). Is this the version that will be available in the U.S.? If not, provide the U.S. Spanish version (with English translation). Provide information on the reading level of this labeling. Do you have data to demonstrate that Spanish-speaking women can read this labeling and use the Reality™ vaginal pouch properly?

Information correcting the above deficiencies should be submitted in the form of an amendment. FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

As noted in our December 6, 1991, filing letter to you, the Obstetrics and Gynecology Devices Panel (the Panel) will meet to review your PMA on Friday, January 31, 1992, at the Crowne Plaza Holiday Inn, Rockville, Maryland. Any update of your clinical study with additional patient data must be received by December 31, 1991, in the form of a PMA amendment. Other additional information to be included in your PMA must be submitted in the form of a PMA amendment and be received by FDA at least 4 weeks (but not less than 3) in advance of the scheduled advisory panel meeting in order for FDA and the Panel to have adequate time to review the new information. Information received by CDRH less than 3 weeks in advance of a scheduled advisory panel meeting will not be considered or reviewed at the meeting.

Page 7 - Dr. Mary Ann Leeper

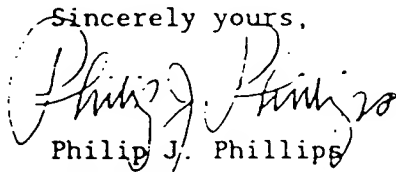
All correspondence regarding this PMA should be submitted in 25 copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application, or questions arising from any response to this letter, may result in additional deficiencies being identified. These will be communicated to you as soon as possible. We will also share with you, as soon as available, the safety and effectiveness questions about your device that will be posed to the Panel for discussion purposes at the Panel meeting.

If you have any questions concerning this deficiency letter, please contact Mr. Colin M. Pollard, at (301) 427-1194 or Ms. Kathy Poneleit Lundsten at (301) 427-1186.

Sincerely yours,



Philip J. Phillips  
Director  
Program Operations Staff  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

DEC 24 1991

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850MANUFACTURING SECTION DEFICIENCY LETTER  
ORIGINAL OR SUPPLEMENT

Mary Ann Leeper, Ph.D.  
Director of Development  
Wisconsin Pharmacal Company, Inc.  
P.O. Box 198  
Jackson, WI 53037

Re: P910064  
Reality Vaginal Pouch, WFC-333, Female Condom

Dear Dr. Leeper:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above-named premarket approval application (PMA). Simultaneously, with review by the Office of Device Evaluation (ODE), the Office of Compliance and Surveillance (OCS) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the medical device GMP regulation.

The Division of Compliance Programs (DCP) of OCS has reviewed the manufacturing section of your PMA and believes that it lacks information necessary to effectively complete a review and determine whether to initiate a PMA inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected, they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. We request that you respond as indicated. Please be advised that continued review by OCS and ODE of your application and/or response to this letter may result in additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment. FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g).

You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

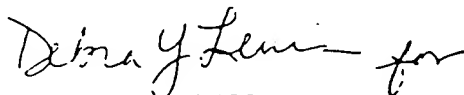
All correspondence regarding this PMA should be submitted in 3 copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter, may result in additional deficiencies being identified.

If you have any questions concerning this deficiency letter, please contact Frank Twardochleb at (301) 427-1128.

Sincerely yours,



Philip J. Phillips  
Director, Program Operations Staff  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

cc:  
HFZ-331 (DCP)  
HFZ-332 (MQAB)  
HFZ-401 (DMC)  
HFZ-402  
BFZ-HFZ-470 (YIN)  
BFR-MW300 (MIN-DO)

## LIST OF DEFICIENCIES

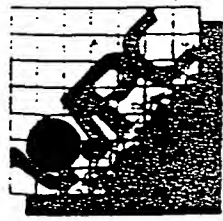
The Office of Compliance and Surveillance (OCS) in the Center for Devices and Radiological Health (CDRH) has completed an initial review of your original premarket approval application (PMA) P910064, dated October 28, 1991, with regards to Good Manufacturing Practices (GMP). Please address the following issues and provide the requested documentation, where applicable:

1. Describe your GMP training program, how it is implemented and how it is documented.
2. The PMA states that Quality Assurance personnel perform planned and periodic audits of manufacturing. State who will perform the audits, and what type of audit training they have received. Discuss who audits the quality assurance section in order to maintain independence from functions being audited.
3. Address particulate monitoring. Discuss any testing which is part of your overall environmental control system. Please provide specifications and procedures.
4. Describe what type of contamination control procedures you have established to prevent contamination of devices by rodenticides and insecticides. Provide the procedures, and a copy of the schedules and certifications, where applicable, for cleaning, pest control, sewage, refuse disposal and removal of hazardous materials.
5. Provide all component acceptance/rejection specifications and procedures, to include SP-201, 203, 205.
6. Describe who manufactures the ring components, and the manufacturing process.
7. Provide a sample of the Receiving Record, and an example of a Product Tracer Card.
8. Provide a manufacturing flow chart, which details each step in the manufacturing process.
9. Describe how the polyurethane sheets are manufactured and provide the process validation protocol.
10. Provide a copy of the specifications and procedures for the die cutting process and heat sealing. The PMA states that the in-process validation is the water-leak testing of three random pouches. Discuss the statistical rationale for this means of validation. Describe the water-leak test and its specifications. Address why the die cutting machine would need adjustment if the range was properly validated.

- Provide a copy of the specifications and procedures for the outer ring application. Address the specific temperature and times utilized. Describe the seal pulling test and the specifications used. Discuss the seal test acceptance/rejection rate. Describe any period of high rejections, as well as, corrective actions taken. Discuss any time when the heat sealer was not properly functioning and any defective products that may have been released. Provide documentation and describe what actions you took to assure released devices were within specifications. Discuss the outer ring application validation protocol and the statistical rationale.
12. Provide a copy of the specifications and procedures for the helium leakseeker test. Address the calibration of the leakseeker. Discuss what the acceptance/rejection rate is. Describe any period of high rejections, as well as, corrective actions taken. Discuss any time when the leakseeker was not properly functioning and any defective products that may have been released. Provide documentation and describe what actions you took to assure released devices were within specifications. Discuss the leakseeker validation protocol and the statistical rationale. Describe why the leakseeker requires standardization prior to use and every two hours if the process has been validated properly. Discuss the leakseeker's pass/fail criteria, listing the specific criteria. Describe why a reading greater than one is considered a failure and how this correlates with hole size, as well as, the size of STDs and the HIV virus.
  13. Provide a copy of the specifications and procedures for the ring insertion, lubrication and pouching processes. Address the processes validation and provide a copy of the protocol, to include the heat sealing of the pouch. Describe the specific temperature, pressure and dwell time of the heat sealer.
  14. Describe all processes which you have validated. Provide validation procedures, and verification of their implementation, for all manufacturing and testing processes.
  15. Provide all specifications, including specific ranges, for all device testing and manufacturing processes.
  16. Address all finished device testing, to include finished device testing after packaging. List the specific acceptance criteria and the rationale behind the acceptance criteria.
  17. Discuss the stability program. List the specified intervals, dimensions, tensile strengths, and burst pressures, as well as, the criteria and results to date.
  18. Justify the sample levels and sample sizes for all tests and inspections performed. Describe how MIL-STD-105D was applied.
  19. Discuss the rationale for measuring the polyurethane film thickness.
  20. Describe the automated measuring instruments. Discuss the tensile

testing and burst testing, include specifications, criteria, procedures and validation information.

21. Describe how the burst tester is calibrated.
22. Address in more detail investigations and actions taken when finished products, after distribution, did not meet performance specifications.
23. Describe and discuss any "latex-like" reactions or hypersensitivities due to the polyurethane.



**Wisconsin  
Pharmacal  
Company**

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FDA date : 12/30/91

*Unsubstantiated 001*

*Clinical update*

**PART I**  
**USE-EFFECTIVENESS**  
**UPDATED INTERIM REPORT**

**PMA-P910064 SUP001    -    12/27/91**

**PART II**  
**USE-EFFECTIVENESS**  
**DATABASE UPDATE**

PMA-P910064 SUP001 -- 12/27/91

PACKAGE TRACKING NUMBER  
8191036022

QUESTIONS? CALL 800-238-5355 TOLL FREE.

SHIPMENT DATE	12/27/91
MASTER LABEL NUMBER	8191036022
2 OF 5	9971985457
DESCRIPTION	P-1/20850
2 OF 5	9971985466
DESCRIPTION	
4 OF 5	9971985475
DESCRIPTION	
5 OF 5	9971985484
DESCRIPTION	
OF	9971985493
DESCRIPTION	
SPECIAL RATE PLAN: 1991 F.B.O. OFFER 841	
To be filled in some areas **Call for delivery schedule	

SENDER'S COPY

COUNT NUMBER 3		DATE 12/27/91	
Your Phone Number (Very Important) 312 280-2281		To (Recipient's Name) Please Print Dr. William Yin	
Department/Floor No		Company Food & Drug Administration	
VIGAN AVE STE 2208		860 1st Street NW	
State IL		City Washington, DC	
ZIP Required 60611		ZIP Required 20850	
IF HOLD FOR PICK-UP, Print FEDEX Address Here			
No. 3		City State ZIP Required	
DELIVERY AND SPECIAL HANDLING (Check services required)		SERVICE CONDITIONS, DECLARED VALUE AND LIMIT OF LIABILITY	
1 <input type="checkbox"/> HOLD FOR PICK-UP (1-2 days)		Use of this card constitutes your agreement to the service conditions in our Current Service Guide, available upon request. See back of package for details.	
2 <input checked="" type="checkbox"/> DELIVER SATURDAY (1-2 days)		We are not responsible for any claim in excess of \$100 per package unless you declare a higher value on this card.	
3 <input type="checkbox"/> DELIVER MONDAY (1-2 days)		An additional charge will be assessed for delivery on any day other than the day specified on this card.	
4 <input type="checkbox"/> DANGEROUS GOODS (1-2 days)		Maximum amount insured for any one package is \$100.00. Federal Express Service Guide applies. Your shipper is responsible for insuring the contents of the package.	
5 <input type="checkbox"/> OTHER SPECIAL SERVICE		Total Charges	
6 <input type="checkbox"/> SATURDAY PICK-UP (1-2 days)		Other 1	
7 <input type="checkbox"/> SATURDAY DELIVERY (1-2 days)		Other 2	
8 <input type="checkbox"/> HOLD FOR PICK-UP (1-2 days)		Total Charges	
9 <input type="checkbox"/> SATURDAY PICK-UP (1-2 days)		REVISION DATE 4/90	
10 <input type="checkbox"/> SATURDAY DELIVERY (1-2 days)		PART 1119000 FORM 7/90	
11 <input type="checkbox"/> HOLD FOR PICK-UP (1-2 days)		FORMAT 807	
12 <input type="checkbox"/> HOLD FOR PICK-UP (1-2 days)		027	
13 <input type="checkbox"/> HOLD FOR PICK-UP (1-2 days)		© 1990 FEDEX PRINTED IN U.S.A.	

F.F. Tracking arrived OK. 355 and gave AirBill # 8191036022

FDA recipient



Ed date: 1/9

January 8, 1992

VIA FEDERAL EXPRESS

Lillian Yin, Ph.D.  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Dear Dr. Yin:

Re: PMA P910064 SUP 002

Enclosed are 25 copies of the responses to the questions sent to Wisconsin Pharmacal in FDA's letter of December 18, 1991.

In the letter, FDA stated that if the responses were to be considered by the Device OB-GYN Advisory Panel at its meeting on January 31, 1992, the responses were due to FDA not less than three weeks prior to January 31, 1992. This submission is sent to meet that deadline.

Sincerely,

Mary Ann Leeper, Ph.D.  
Director of Development

MAL/dlp

Enclosures: Twenty-five sets of two-volumes

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

301  
FDA date: 1/15  
Omead cc2

REALITY  
PMA - P910064 - SUP002

FDA QUESTIONS AND WPC RESPONSES  
JANUARY 8, 1992

Table of Contents

Page No.

Device Materials and Biocompatibility

Question No. 1 and Answer 1-3

- Attachment 1A - Water-Based Lubricant
- Attachment 1B - Oil-Based Lubricant
- Attachment 1C - OTC Vaginal Drug Monograph, October 1983
- Attachment 1D - USP/CTFA Description of Ingredients

Question No. 2 and Answer 4-7

- Attachment 2A - Sensitization Assay - Summary
- Attachment 2A-1 - Dermal Sensitization Report and Protocol  
(Including Positive Control) on Film Applied  
Directly to Skin
- Attachment 2A-2 - Dermal Sensitization Report and Protocol  
(Including Positive Control) For Oil Extract
- Attachment 2A-3 - Dermal Sensitization Report and Protocol  
(Including Positive Control) For Saline Extract
- Attachment 2B - Toxicological Opinion from Dr. Karl Gabriel,  
BioSearch, Inc.
- Attachment 2C - Long-Term Vaginal Irritation Study - Summary
- Attachment 2C-1 - Long-Term Vaginal Irritation Draft Report and  
Protocol for Beads



# Wisconsin Pharmacal Company

A L I T Y     ◊     I N N O V A T I O N

January 29, 1992

VIA FEDERAL EXPRESS

Mr. Colin M. Pollard  
Food and Drug Administration  
Center for Devices and Radiological Health  
1390 Piccard Drive (HFZ-470)  
Rockville, Maryland 20850

Dear Colin:

Enclosed is the Wisconsin Pharmacal presentation on **Reality PMA** (P910064) for the OB-GYN Devices Panel review, 1/31/92. This is inclusive except for two presentations: Drs. B. Voeller and M. Silverman. If I can, I will give you copies of Bruce Voeller's presentation on Thursday. Dr. Silverman's is "informal."

If you need any other information, please call me at the Holiday Inn Crowne Plaza Hotel.

See you on the "big" day!

Thanks for your help.

Sincerely,

Mary Ann Leeper, Ph.D.  
Director of Development

MAL/dlp

Enclosures - 30 sets of OB-GYN Devices Panel 1/31/92 Presentation

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541, Fax: (312) 280-9360

# FAMILY HEALTH INTERNATIONAL

January 29, 1992

Mary Ann Leeper, Ph.D.  
Phoenix Healthcare, Inc.  
919 N. Michigan Avenue  
Suite 2208  
Chicago, IL 60611

Re: Authorization to MAF-421

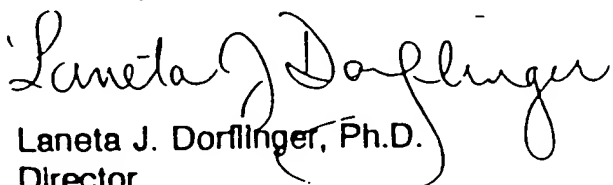
Dear Dr. Leeper:

This letter authorizes the Food and Drug Administration to include by reference information in Amendment 2 to our device master file (MAF-421) for your premarket approval application (P910064) for the Reality vaginal pouch. This amendment was submitted by us on January 29, 1993, and contains information on coital frequencies and data pooling.

Authorization to cross-reference MAF-421 was originally given on September 24, 1992 in a letter from Mr. Robert Hughes to Dr. Mary Ann Leeper.

If you have any questions regarding this, please contact me at (919)544-7040 ext. 449.

Sincerely,



Laneta J. Dorfinger, Ph.D.  
Director  
Regulatory Affairs and Quality Assurance

LJD/smk

**FHI**

*Headquarters:*  
P.O. Box 13950  
Research Triangle Park, NC 27709 USA  
Telephone: 919-544-7040

*AIDSCAP Division:*  
2101 Wilson Boulevard, Suite 700  
Arlington, VA 22201  
Telephone: 703-516-9779 . Fax: 703-516-9781  
Voice Mail: 703-516-0460



# Wisconsin Pharmacal Company

February 24, 1992

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Dear Dr. Yin:

Re: Reality Vaginal Pouch (WPC-333)

Enclosed are three copies of the IDE to perform the Rip/Tear Study as requested by the OB-GYN Devices Advisory Panel at the January 31st review of the Reality PMA.

Dr. Pearlmuter requested we repeat the first study carried out on Reality (1988) but using the 170 mm length devices.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosures

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



**Wisconsin  
Pharmacal  
Company**

QUALITY ♦ INNOVATION

2/26/92

February 25, 1992

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
Food and Drug Administration  
Division of Obstetrics/Gynecology, Ear, Nose, Throat & Dental Devices  
(HFZ-470, Room 240)  
1390 Piccard  
Rockville, Maryland 20850

Dear Dr. Yin:

I appreciated receiving your call on Friday afternoon. In that call, you indicated that at this time there was no need for FDA representatives to meet with representatives of Wisconsin Pharmacal Company (WPC) as I had requested in my letter of February 11, 1992. You stated FDA and WPC were not in an adversarial position regarding approval of the **Reality** vaginal pouch/female condom. You also asked that WPC refrain from submitting anything to you regarding the Advisory Panel meeting of January 31, 1992, until we have received a letter from you that would summarize FDA's position. You estimated that this letter would be completed in a week to ten days.

My initial reaction was to wait for your letter, assuming it would reflect the Advisory Panel recommendations, and then respond accordingly. Given past events, however, I have serious concerns. I believe it is important that I state these concerns directly to you as soon as possible. The regulatory history of this product has been marked by ever-changing regulatory requirements and by what appears to be a bias against approval. In view of this, my objective is to reach a constructive understanding between FDA and WPC regarding precisely what is required for final approval.

As you know, Wisconsin Pharmacal (WPC) is a small, specialty consumer products company. The development of **Reality** is the first project ever undertaken by WPC to bring a regulated medical device to market.

Because of WPC's concern to develop *Reality* in the best way possible, the President of WPC, John Wundrock, myself, and others from WPC met with FDA in December, 1987, to get guidance and direction as to how to proceed to meet all of FDA's requirements.

We proceeded to implement the directions of FDA, including pre-reviews by FDA of clinical protocols and safety data.

The history is familiar to you. We implemented the studies based on the agreement at the December, 1987, meeting that *Reality* was substantially equivalent to a male condom; and about one year later made a 510(k) submission. FDA responded that "they made a mistake"; that *Reality* was not to be treated like a male condom, that it was substantially different and thus a new classification was necessary, along with new guidelines that did not yet exist. New guidelines were discussed at an August, 1989, OB-GYN Devices Panel Meeting. The Chairperson of the Panel, at the conclusion of the sessions (see Attachment A), was quite specific with me as to what the Panel recommended guideline requirements were, including the requirement of a 200 women follow up for six-months pregnancy use-effectiveness study. The Panel's stated objective with this approach was to expedite the approval of new female controlled barrier devices that would help to protect against STDs.

In October, 1989, we met with you and your staff. In that meeting, you argued in favor of a 12-month use-effectiveness study involving 200 women. WPC argued that a six-month study as recommended by the Advisory Panel was sufficient and that efficacy could be shown in a six-month or less study. You warned that if we were not comparable to other barriers at six months, we risked not obtaining approval. We accepted that risk, particularly because USAID agreed to fund only a six-month study and because a larger study would substantially delay submission of a PMA (incremental 2-3 years). FDA and WPC also agreed at that meeting that other studies would be necessary, specifically a vaginal trauma study, an instruction study and a permeability study. Studies previously submitted to FDA were considered adequate to satisfy Phase I requirements. There was no indication that a second rip/tear study would be required. This October, 1989, meeting was highly relevant since the development of *Reality* had been initiated and most of the Phase I work had been completed approximately two years before the draft guidelines were issued. Our agreement of October, 1989, was confirmed in writing (Attachment B). It should be noted that FDA did not finalize its guidelines until April, 1990, six months later.

Wisconsin Pharmacal proceeded to complete the additional requirements. We supported the development of new technology to meet FDA's permeability study requirements, including several sub-studies because FDA reviewers could not decide among themselves what was needed. We completed the additional clinical studies and, together with FIII, CONRAD, and USAID initiated the six-month Phase II Pregnancy Use-Effectiveness Study.

We proceeded in good faith believing that the program as agreed with FDA in October, 1989, would be acceptable. FDA approved all necessary IDEs, including that necessary for a six-month study.

As clearly stated at the August, 1989, Advisory Panel meeting, our October session (reflected in the letter), and in the stated guidelines, the Reality PMA could be submitted earlier than completion of the pregnancy study under the condition of comparable results to historical controls; e.g., life-table failure rate of  $\leq 20$ .

We were always prepared to file as soon as possible. We felt we had that direction from the August, 1989, Panel session and the FDA October, 1989, meeting; the rationale being -- safety is established and if efficacy is at least comparable, it was important to give women the opportunity to protect themselves from AIDS and other STDs. The risk/benefit was balanced in the public interest to make the product available.

In June, 1991, we determined that we would do an interim analysis of the pregnancy data and decided in September, 1991, to proceed to file the PMA. As you are aware, I called, faxed, and sent letters to you and Colin Pollard requesting a meeting to review the PMA filing strategy. I was advised that "it was not necessary."

We filed the PMA on October 29, 1991. I again requested by phone, fax, and mail that we meet with FDA to review the PMA to make sure the filing was understood. I was told "it was not necessary." Upon hearing that the PMA would be accelerated for 1/31/92 Panel review, I was encouraged because it appeared FDA was prepared to expedite approval in accord with our prior understanding. I again formally requested (phone, fax, and mail) that we meet with FDA in advance of the session so that there would be no surprises for either FDA or WPC. I was told "it was not necessary."

On January 31, 1992, WPC was startled at FDA's presentation of our data and more important the apparent negative bias of FDA's presentation and comments throughout the day.

Key WPC concerns regarding the January 31, 1992, session include:

- On one hand, FDA indicated **Reality** was not the same as the male condom and we must develop new technology and standards and submit a PMA. Yet, at the meeting, the FDA reviewers questioned our data because the **Reality** product materials behave differently than latex male condoms; i.e., polyurethane is not elastic, elongation is not a germane specification.
- The Guidelines state the vaginal pouch has to be comparable to historical controls, specifically cap, sponge, or diaphragm. Our data shows that **Reality** is comparable. But, at the meeting, FDA reviewers questioned comparability because the cap, sponge, and diaphragm don't protect against STDs.
- When FDA asked for a male condom comparison in December, 1991, I told them relevant male condom data doesn't exist - the response to me was "we know but keep looking." In fact, this was known when the Advisory Panel reviewed FDA's proposed guidelines in August, 1989. Yet, at the January 31st session, the FDA reviewer kept questioning us because we didn't compare to a male condom! (We asked Dr. James Trussell, the renowned statistician in this field, to compare our data to the male condom and other barrier contraceptives via his access to raw data and also his review of the literature. His analysis shows **Reality** to be comparable.)
- In the Phase I studies we actually performed comparison studies to the male condom. The results showed **Reality** to have statistically significant less risk of product failure than the male condom. Yet, the FDA reviewers ignored these results. Indeed, a repeat of the rip/tear study comparing **Reality** to a male condom was requested by the Panel contrary to our earlier understanding with FDA.

- At the January 31st session, FDA reviewers and representatives constantly referred to the August, 1989, Panel recommendation as requiring a 12-month study. FDA and WPC know that is not the case. The transcript of the August, 1989, meeting is clear.
- As reflected in the January 31st transcript, one FDA representative stated at the meeting that **Reality** is worse than the male condom. There are no valid data to support such a statement. There is no well-controlled study for male condom effectiveness comparable to the **Reality** study.
- FDA representatives stated at the January 31st meeting that WPC should have do more permeability studies. The completed studies already have advanced the state of the art and go beyond FDA's previous requests. The two Panel representatives in this area, Drs. Colton and Goldstick, were quite clear that further testing was not necessary. These same Panel members stated that we've established permeability, using state-of-the art technology; that **Reality** blocks against  $\phi 174$ , a viral particle smaller than Hepatitis B. We've established the permeability characteristics. We are happy to clarify any questions, but we strongly question why FDA would suggest the need for more basic research since the permeability of specific male condoms and other devices to which we are required to be comparable have not even begun to be characterized.

I am clear that our submission was not perfect and that there are valid questions that need to be answered. I am also clear that I was naive in submitting the draft labeling as I did. (In essence, I drafted the **Reality** labeling very like the FDA approved labeling for the Today Contraceptive Sponge. I was under the misunderstanding that labeling for devices would be treated very similar to drugs; i.e. negotiated between FDA and the Company after all else is cleared up. This is what we were prepared to do.)

Dr. Lillian Yin  
February 24, 1992  
Page 6

From our perspective, it seems that FDA publicly seeks to reassure the public that it is supportive of new choices of barrier contraceptives that are potentially important to women's health, but internally has set a course to delay or to prevent approval of a female condom\*. Nonetheless, the Panel came to an opinion that Reality is safe and comparable to other barrier methods and unanimously recommended that FDA approve it provided certain conditions were met. These conditions were (1) completion of the Pregnancy Use-Effectiveness Study with 200 women followed for six months and a life-table failure rate of  $\leq 15/100$  women; (2) respond to Dr. Colton's questions on permeability; (3) redo the post use rip and tear study; and (4) modify labeling more like the male condom.

Wisconsin Pharmacal is ready to address the Panel's conditions, as well as to respond to FDA's questions on manufacturing and quality control received in January, 1992. As we proceed, it is essential that we know whether FDA intends to follow the Panel's recommendation. We are prepared to meet with you at your convenience to discuss our concerns and the next steps.

We look forward to your letter and hope that by expressing our concerns we have "cleared-the-air" to allow for a constructive review process.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Attachments

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

\*Reality is the only female condom to complete the guidelines requirements. Two other devices are still at Phase I, years away from submission of a PMA.

**ATTACHMENT A**

(Section of Transcript - August 1989)

1 for possible harmful effects of the device itself that didn't  
2 come out in the six months effectiveness testing?

3 DR. CONNELL: Or pregnancy, or all of the above?

4 DR. DOWNS: Yes, all of the above.

5 MS. PEARSON: Right, but all of the above, from a  
6 consumer's point of view, I don't know what interest the FDA  
7 has in requiring STD data, if the product has come in and done  
8 whatever it takes to do to get approval as a new barrier  
9 contraceptive. And then they're going to do, you know,  
10 contraceptive--STD--is it necessarily the issue any more?

11 Or it's going to have to be figured out in this--  
12 it's not necessarily the FDA's issue, at least the way I  
13 understand postmarket surveillance, and in the experience with  
14 the cervical cap, when the studies that were recommended by  
15 this panel were specific to the device, and to possible harm  
16 from the device that, in the case of the cap, there was some  
17 equivocal indications from the study that you asked to be  
18 followed up on.

19 If there is nothing even hinting at the possibility  
20 of harm, then maybe you don't need a specifically designed  
21 postmarket surveillance, but just the routine that every  
22 manufacturer follows.

23 DR. CONNELL: -I think it's awfully easy to argue  
24 both sides.

25 MR. SHELTON: Well, I guess I want to argue that

1 side. I think six months gives you all you're going to know.

— 2 We're really not going to get information on STDs. The only  
3 thing you're going to get is pregnancy rates, which will serve  
4 as a surrogate for STDs.

5 DR. CONNELL: Are you arguing for another six  
6 months?

7 MR. SHELTON: No, I'm arguing for six months.

8 DR. CONNELL: Over and out?

9 MR. SHELTON: Over and out, yes.

10 DR. CONNELL: Okay, Henry?

11 MR. GABELNICK: The same.

12 DR. CONNELL: Yes?

13 DR. LEEPER: I just wanted to clarify what we had  
14 said earlier--it's kind of repeating what everyone else has  
15 just said--that we had--I thought that we had come to the  
16 consensus that the study was going to be six months. However,  
17 the definition of the study said that if, at some point  
18 earlier than that, less than six months, if we had statisti-  
19 cally valid data--

20 DR. CONNELL: That's right.

21 DR. LEEPER: --that said it was at least 80 percent,  
22 we could go to market.

23 DR. CONNELL: Right.

24 DR. LEEPER: And that we would then complete the  
25 study at six months, and I thought we had all agreed upon

1 that, so I was getting concerned that all of a sudden, the  
— 2 same thing, you were going back to ground zero again.

3 MR. POLLARD: No, I think that's everyone's under-  
4 standing. I think the question went back to the original  
5 premise that pregnancy is going to serve as a surrogate for  
6 STD, and there was a certain element of discomfort.

7 And at the time when the panel said, yes, let's go  
8 that route, there was a general understanding that post-  
9 marketing surveillance--at least, that's the way it was  
10 reading, it seems--was going to look for certain things--that  
11 it was going to somehow get at some of the things they didn't  
12 feel the surrogate end point was going to.

13 DR. CONNELL: Okay, Sheryl, and then David, and then  
14 Henry.

15 DR. RUZEK: I personally feel that I would like to  
16 see a greater variety of studies done, once the device is on  
17 the market, with more diverse populations than you would get  
18 if you continued to look at this very, very peculiar sample of  
19 people that will constitute the FDA study.

20 So, if there is a way we could build in postmarket  
21 surveillance, not to be the continuation of these people, but  
22 that studies be initiated with diverse populations, it would  
23 feel much better.

24 I want to know how this is being used by people out  
25 there, once it's on the market.

**ATTACHMENT B**

(Confirming Outcome of October, 1989, Meeting)



# WISCONSIN PHARMACAL COMPANY

A DIVISION OF BADGER PHARMACAL INC.

2977 HWY 60 P.O. BOX 198, JACKSON, WISCONSIN 53037 PHONE (414) 677-4171

October 18, 1989

Lillian L. Yin, Ph.D.  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

VIA MAIL AND FAX: (301) 427-1977

Dear Dr. Yin:

We greatly appreciated the opportunity to meet with you on October 12, 1989, to discuss the applicability of the draft guidelines for barrier contraceptives to the continued development of WPC-333. We believe it was a productive meeting. As a result, Wisconsin Pharmacal and CONRAD/FIII are now proceeding expeditiously as follow-up on all actions required to begin the studies we discussed.

During our meeting, we reached agreement on the following points:

## Pre-clinical

Following submission of the IDE, FDA will review the pre-clinical work done with WPC-333 to determine if any additional studies are necessary.

## Phase I

Because Wisconsin Pharmacal has already done extensive Phase I trials, we will not be required to do additional studies in the format suggested by the draft guidelines. To supplement work already done, Wisconsin Pharmacal will conduct a detailed study in 15 women to determine possible adverse effects, including vaginal trauma and ulceration, cervical erosion, mucosal irritation, and sensitization. Photographs will be taken. Each study participant will use the device five times on five successive days with specific requirements for the amount of time WPC-333 is worn to determine if repeated stress causes any untoward effects. A study protocol will be submitted as an IDE for review by FDA prior to study implementation.

Lillian L. Yin  
October 18, 1989  
Page 2

### Phase II

A six-month study will be conducted by CONRAD/FIII with the goal to have 200 evaluable women at the end of the study. We recognize that by planning a six-month study rather than a one-year study, we bear the risk that six-month results might result in unacceptable pregnancy rates. We recognize that a six-month study is more rigorous statistically, since method failures typically occur more frequently in the first two to three months of use.

It was agreed that the study results may be submitted to FDA as part of a PMA prior to the completion of the study if the results indicate a minimum efficacy rate of 80 percent at the 95 percent confidence level.

Enrollment, dropout, pregnancy, adverse effects, etc., will be tracked monthly. Life table analysis of the results will be calculated by month.

The study for each patient will begin on enrollment and not at the time of the first coitus. We recognize that if there are insufficient episodes of intercourse in the first month because of the start date, the first month of use might not be suitable for evaluation.

The study for each patient will be concluded following a post determination visit at six months plus two weeks, including a pregnancy test.

A central laboratory in the United States for PAP smears from the U. S. sites will be used. Non U.S. sites will use local laboratories.

A "Level of Acceptability" defined as the participants' and their partners' understanding of the instructions for use and their ability to use the product will be evaluated. It is not intended to refer to whether they "like" or "dislike" the product.

### Post-Marketing Surveillance

There are no specific requirements for post-marketing surveillance. Any recommendations for surveillance will be dependent on study results.

Lillian L. Yin  
October 18, 1989  
Page 3

### Labeling

Following approval, labeling will include a description of studies done to support approval. This will permit health care professionals and consumers to evaluate the data and understand the limitations of the study design. To the extent actual efficacy rates for WPC-333 are included in the labeling, comparison to existing products will also be included to provide perspective.

I have tried to fairly represent our points of agreement during the meeting. If you believe I have missed a point, it would be appreciated if you would promptly bring it to our attention so that there is no confusion at a later time.

Again, our thanks for the meeting and your assistance.

Sincerely,



Mary Ann Leeper, Ph.D.  
Development, WPC-333

MAL/dlp

Food and Drug Administration  
1390 Piccard Drive  
Rockville MD 20850

MAR 26 1992

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development  
Wisconsin Pharmacal Company, Inc.  
919 North Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

RE: P910064  
Reality<sup>™</sup> Vaginal Pouch  
Filed: October 29, 1991  
Amended: December 17, 19 and 30, 1991, and January 9, 15, and 31, and  
February 26, 1992

Dear Dr. Leeper:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its scientific review of the above referenced premarket approval application (PMA). The Obstetrics-Gynecology Devices Panel, which also reviewed your PMA, recommended to CDRH at the January 31, 1992, panel meeting that the PMA be considered approvable subject to the submission and review of certain additional data. We agree with the Panel that additional data are needed to complete our review and to determine whether there is reasonable assurance that the device is safe and effective for its intended use. Thus, your PMA is not approvable at this time.

When we receive this additional information, the expedited review of your PMA will be continued. In order to continue the review process, we have listed the following questions which require responses as indicated. Most of the questions follow directly from the data requests made in our December 18, 1991, deficiency letter to you, and discussions of your data at the January 31, 1992, Panel meeting. Upon receipt of an amendment fully addressing the requests listed below, expedited review of your PMA will resume.

Summary of Safety and Effectiveness

1. Revise the comprehensive Summary of Safety and Effectiveness Data to provide sufficient detail of all safety and effectiveness information, including all relevant preclinical and clinical studies as completed. This section should also contain conclusions drawn from the studies for each claim of device safety and effectiveness.

Revised and Updated Technical Section (Preclinical and Clinical)

2. Revise the technical sections of your PMA, both the preclinical and clinical, to include a complete description of all studies; the objectives of the studies; data from the studies and how it was

analyzed; and conclusions from the studies, including positive, negative and inconclusive results. (The Panel, at various points during the January 31, 1992, meeting, recommended that particular sections be revised accordingly - see transcripts.)

Device Materials and Biocompatibility

3. Water-Based Secondary Lubricant

- a. Identify the function (e.g., preservative, stabilizer, etc.) of each ingredient in the lubricant.
- b. Provide biocompatibility data from the literature on all ingredients in the lubricant.
- c. Provide biocompatibility data on the final product (water-based secondary lubricant) to support its safe use. This should include the following:
  - i. mucosal irritation;
  - ii sensitization;
  - iii. mutagenicity;
  - iv. acute and chronic systemic toxicity; and
  - v. teratogenicity.
- d. Provide data demonstrating that the water-based secondary lubricant, at the time of manufacture and after storage, conforms to the microbiological specifications identified in Attachment 1A of your January 8, 1992, amendment.

4. Provide a justification for providing an oil-based secondary lubricant for the Reality™ Vaginal Pouch, when you state on page 2 of your January 8, 1992, amendment that "Oil-based lubricants are not recommended for vaginal intercourse." The only intended use considered by FDA for the Reality™ Vaginal Pouch is for vaginal intercourse.
5. Clarify which company supplies the polyether polyurethane rings. Your PMA application states on page 304 that the inner and outer rings are supplied by Chartex International while your master file states on page 85 that the inner and outer rings are supplied by Guenther Schuster Stanik, Co.
6. Provide a copy of the final report of the Long-Term Vaginal Irritation Studies conducted on the Reality™ Vaginal Pouch.
7. Provide quantitative data documenting the detectable levels of methylene dianiline (MDA) in your final product, at the times of manufacture and proposed shelf-life. Also, provide a detailed description of the sample preparation, methodology for detecting MDA, and validation of that methodology.

8. Provide a comprehensive carcinogenicity risk assessment, based upon the detectable levels of MDA in your final product, at the times of manufacture and proposed shelf-life, and the expected device use.

Device Physical Properties and Characteristics

9. Provide the following information on the physical properties of your final product:
  - a. a detailed description of the air burst pressure test, including diagrams of the apparatus, and air burst volume data on the final product; and
  - b. elongation data on the final product. Ring or dumbbell specimens may be used, but the specimen must include the seam of the sheath.

It was noted that the proposed specifications for the length of your device is 170 millimeters  $\pm$  10 millimeters (page 367 of your PMA application). The proposed revision of the International Organization for Standardization (ISO) specifies a minimum acceptable length of 170 millimeters for latex condoms. In light of the proposed ISO specifications, provide a justification for your proposed specifications.

10. Provide the following information on the seam of the sheath:
  - a. a detailed description of the seam welding process;
  - b. data from a parametric study of the seam welding process which demonstrates that the optimal welding parameters have been used;
  - c. data on the normal variations of the above parameters and their effects on the seam strength;
  - d. photomicrographs of the seam at greater magnifications (200-300X); and
  - e. elongation data on the sheath including the seam. (See deficiency number 9.)
11. Provide a detailed description of the processes used to bond the outer ring to the sheath, and data on the strength of this bond.

Shelf-Life

12. Provide data from real-time aging studies to demonstrate the chemical stability of the device materials (polyurethane and lubricant) at your proposed shelf-life. This data should include the following information:
  - a. molecular weight and gel molecular number for the device material;

- b. data on physical properties (i.e., tensile strength, break force, elongation, and air burst pressure and volume) of the device;
- c. data on the physical performance and characteristics of the inner and outer rings after aging, including the stiffness of the outer ring; and
- d. data on the bond strength and integrity of the outer ring to the sheath.

Barrier (Transport) Studies - The Bacteriophage ( $\phi$ X174) Study

13. Provide a complete description and data, including standard error values, for all control experiments which were conducted to assure against false negative data. This should include the following:
- a. data from additional experiments to determine the effect of the surfactant, Tween 80, on the challenge virus  $\phi$ X174;
  - b. a detailed description of the experiments and data which were conducted to determine whether components of the testing apparatus and procedure inactivated the challenge virus  $\phi$ X174. Was the restraining sock tested in these experiments?; and
  - c. a detailed description of the spiking experiments which should include the following information:
    - i. whether the entire test procedure, including pulsed pressure, was used; and
    - ii. whether there was challenge virus  $\phi$ X174 on the "upstream side" during testing, which might penetrate through to the "downstream side."

In addition, discuss how the results of the above experiments may affect the interpretation, including sensitivity and reliability, of test data from vaginal pouches with and without intentional holes.

14. Provide data on the titers of the challenge virus  $\phi$ X174 ("upstream side") at the beginning and end of each test, and provide the original assay and reassay data from penetration tests ("downstream side") for all intact vaginal pouches. Using these data, justify the conclusion that there was no evidence of virus penetration for each intact vaginal pouch tested.
15. Provide data for intact latex male condoms which were tested, and justify your conclusions for these experiments.

16. Provide data on the profile of pressure at the surface of the vaginal pouch as a function of time for at least four cycles of the pulsed pressure application.
17. Determine the sensitivity of your test method for detecting small holes, and include all calculations and graphs. Also, address whether you determined the sizes of the laser-induced holes (entrance and exit) on vaginal pouches actually tested. Compare your results to those found in FDA's laboratory testing of latex condoms (See Retta et.al. "Test Method for Evaluating the Permeability of Intact Prophylactics to Viral-Size Microspheres Under Simulated Physiologic Conditions," Sexually Transmitted Diseases, 1991; 18:11-118).

To adequately demonstrate that your device performs as well as latex condoms, data must show that your test method is capable of detecting leakage through holes of 5 microns or less. This will permit comparison to FDA's laboratory data on latex condoms. Is your test method capable of this sensitivity? Finally, discuss the barrier properties of your device to those of conventional latex condoms, as required in the guidelines, entitled "Premarket Testing Guidelines for Female Barrier Contraceptive Devices Also Intended to Prevent Sexually Transmitted Diseases" (page 2).

18. Clarify whether or not the Dulbecco's phosphate buffer included calcium chloride, and if so, at what concentration.

#### Quality Assurance Control Procedures

##### 19. Water Leakage Test

- a. Provide data to support the proposed fill volume for your device.
- b. Revise your water leakage test methods to parallel the methodology FDA employs to detect pinholes in latex condoms, the filled device is allowed to hang for a minute, taken down from the fill-tube, twisted closed, and rolled on a towel to look for wet spots. This method helps to ensure that holes in the top/open end of the device are found with equal sensitivity to those at the closed end.

It was noted upon review of your water leakage test that leakage at a distance of 16 millimeters or less from the rim (open end) of your device may be disregarded. Considering this, provide a description of the procedures that will be used to assure the integrity of this portion of your device.

##### 20. In-Line Helium Gas Leak Test

- a. Provide additional data to demonstrate the validity and sensitivity of your in-line helium gas leak test. This should include the following:

- i. a detailed description of the in-line helium gas leak test;
- ii. the number of devices with and without intentional laser induced holes tested, and raw data from those tests;
- iii. information on whether or not the sizes of the laser-induced holes (entrance and exit) on vaginal pouches actually tested were determined; and
- iv. calculations and graphs used to determine sensitivity.

Validation of the in-line helium gas leak test should be described and done using the exact procedures that will be used during your on-line testing. Were original validation data presented in your PMA determined by thermal conductivity or by pressure differential across the membrane?

#### Clinical and Statistical

#### 21. Phase I - Feasibility Studies

- a. Reanalyze the risk exposure rates for the Reality™ Vaginal Pouch and the male condom in the Post-Coital Leak Test (Study 2) by excluding all study subjects who experienced device displacement and discontinued intercourse, or who experienced device displacement and continued intercourse without the device, from the denominator of the exposure rate. Also, provide an example calculation of the probability of risk failures for the Reality™ Vaginal Pouch and the male condom, and identify any union events (if applicable).
- b. Provide justification for combining data from the Post-Coital Leak Test (Study 2) and the Dislodgement Studies (Studies 3 and 4) to calculate the combined probability of risk for the Reality™ Vaginal Pouch and the male condom (Table IV-5).

#### 22. Phase II: Effectiveness Study - Pregnancy Use-Effectiveness

Please be advised that your Phase II: Effectiveness Study - Pregnancy Use-Effectiveness does not meet the recommendation specified in the guidelines, entitled "Premarket Testing Guidelines for Female Barrier Contraceptive Devices Also Intended to Prevent Sexually Transmitted Diseases (STDs)." The guidelines recommend a study sample size and duration of at least 200 study subjects, contributing to a standard 12-month lifetable analysis. We have reviewed the transcripts from the January 31, 1992, Panel meeting. These transcripts do not resolve our current concern regarding your study methodology.

Your PMA qualified for the guidelines and expedited review because there are no woman-controlled alternatives for barrier protection from STDs. Therefore, in the absence of alternatives, we have determined that your limited clinical study (i.e., 200 women for 6 months) may only be sufficient to demonstrate a relative effectiveness for protection from

STDs. Because of these study limitations, a contraceptive claim cannot be supported when there are commercially available barrier contraceptive devices that have been fully evaluated with long term, well-controlled clinical studies.

In order for us to complete our review of your study, using pregnancy as a surrogate endpoint, to demonstrate the effectiveness of your device to prevent STDs, address the following review concerns.

- a. Provide a monthly lifetable analysis of safety and effectiveness data (i.e., pregnancies rates and discontinuation rates) for the pregnancy use-effectiveness study with at least 200 women completing the study for 6 months. These data should demonstrate that the pregnancy rate for the completed study is no higher than the interim analysis (15.1 pregnancies per 100 women for 6 months) presented in your December 30, 1991, amendment.

- b. Provide a monthly lifetable analysis of pregnancies rates from the pregnancy-use effectiveness study according to user and method failures, and according to parous history of the study subjects.

Also, provide data from the completed pregnancy use-effectiveness study on a floppy disk (ASCII or Database file (DBF) format). These data should include the subject identification number, center enrolled, inclusion or exclusion from the efficacy study, date enrolled, date last contacted and method of contact, date discontinued the study and reason for discontinuation, dates of chemical pregnancy tests and results, and clinic visits.

- c. Provide a complete description of women who discontinued the study. This should include any follow-up pregnancy tests and results from those tests, as well as the numbers of women who did not have pregnancy tests. Discuss how these data may or may not influence the results from the pregnancy use-effectiveness study.
- d. Provide a complete description of all women who had multiple reasons for discontinuing the pregnancy use-effectiveness study (e.g., personal reasons and accidental pregnancy), and which of the competing reasons was ultimately identified as the factor for discontinuation.
- e. Provide justification for pooling data across the centers.

## 23. Additional Performance Data

Provide data from a clinical study on the performance (i.e., breakage, leakage) of the device, as assessed by post-coital testing, such as your validated water leakage test. Provide a rationale and justification for your method of post-coital testing and sample size.

Device Labeling

24. Provide revised patient labeling to accurately reflect the findings from the preclinical and clinical studies on the Reality™ Vaginal Pouch (see enclosures).
25. Provide directions for use for the Reality™ Vaginal Pouch in your labeling and include the following:
  - a. the maximum duration the device should remain in place and how soon after coitus the device should be removed; and
  - b. identification of whether the device is intended for one coital episode or for multiple coital episodes.

Provide data from your clinical studies to support the above recommendations regarding length of device wear and use.

Please be advised that the directions for use should assure safe and effective use of the device, and should not exceed the seventh grade reading comprehension level (see enclosures).

In addition to the above, the Division of Compliance Programs of the Office of Compliance and Surveillance has reviewed the manufacturing section of your PMA, and believes that it lacks information necessary to effectively complete a review and determine whether to initiate a PMA inspection. We request that you respond to these deficiencies, as identified in our letter of December 24, 1991. Once these deficiencies have been adequately addressed, an FDA inspection must find that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820).

As outlined in the preceding pages of this letter, extensive data are still needed for your PMA. Because of the expedited nature of this PMA review process, many of these data were not available when CDRH and the Obstetrics-Gynecology Devices Panel considered your PMA in January. In particular, these data are needed, in their entirety, to adequately assess both risk-benefit and patient labeling. Therefore, even though your response will be treated as a major amendment to the PMA, we will resume expedited review of your PMA upon receipt of this amendment. We will schedule a meeting of the Obstetrics-Gynecology Devices Panel to complete the review of your PMA.

We would like to hear from you on your plans to submit the required amendment, so that we can make the necessary logistical plans for scheduling the Panel meeting. We are hopeful that we can work together to continue the expedited review of your PMA to further our mutual interest in public health.

You will be notified of the location and date of this meeting. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 4 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting.

Page 9 - Dr. Mary Ann Leeper

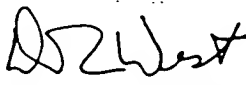
As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension, and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information (25 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

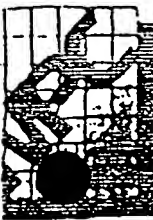
PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

If you have any questions concerning this deficiency letter, please contact Mr. Colin Pollard at (301) 427-1180 or Ms. Kathy Poneleit Lundsten at (301) 427-1186.

Sincerely yours,

  
for Robert L. Sheridan  
Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosures



# Wisconsin Pharmacal Company

A L I T Y   ♦   I N N O V A T I O N

March 31, 1992

VIA FAX AND FEDERAL EXPRESS

Mr. Colin Pollard  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Dear Colin:

Re: Reality Vaginal Pouch (WPC-333)

Since you were not available, I related to your secretary that another three copies of the IDE for the Rip/Tear Study would be forwarded to you. They are enclosed. I have also attached previous communications to you which show that FDA did receive this same IDE on February 25, by M. Courtney, at 10:16 in the morning.

Since FDA has had the IDE for over 30 days, I'm sure that you will see that the review is completed as quickly as possible so we can get the study started. While the 30-day time limit has expired, we choose to wait for FDA's input and hope that it will be received very soon.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosures

CC: Dr. Lillian Yin

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



# Wisconsin Pharmacal Company

U A L I T Y    ♦    I N N O V A T I O N

April 10, 1992

VIA FAX AND FEDERAL EXPRESS

Mr. F. Alan Andersen, Acting Director  
Office for Device Evaluation  
U. S. Food and Drug Administration, HFZ-400  
1390 Piccard Drive  
Rockville, Maryland 20850

4/13/92

Dear Mr. Andersen:

Re: Reality Vaginal Pouch (WPC-333), PMA-P910064

This is to acknowledge receipt of a letter from Mr. Sheridan dated March 26, 1992, relating to the above-referenced PMA. We are evaluating the specific technical comments in the letter and will address the issues raised as soon as possible. Our submission will provide detailed information and/or commentary as appropriate.

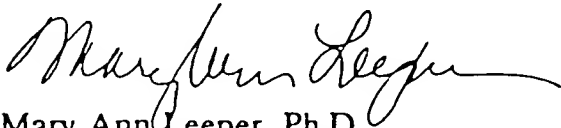
We are pleased that FDA will continue expedited review of our submission(s). Expedited review is important because women do not have under their control a barrier device that can be used to reduce the risk of unintended pregnancy and sexually transmitted disease, including AIDS. Availability of a vaginal pouch will permit women to have this choice.

We were surprised by the statement that FDA intended to schedule a meeting of the Obstetrics-Gynecology Devices Panel to complete review of the PMA. At the January 31, 1992, Advisory Panel meeting, the Panel unanimously recommended approval subject to certain conditions. The most important of these conditions was that the six-month use-effectiveness study be completed by 200 women and that the life-table pregnancy rate be equal to or lower than 15 (preliminary analysis of unaudited data from the completed study indicates that the pregnancy rate is substantially below 15.) If these conditions were met, neither the Advisory Panel nor FDA appeared to contemplate a further meeting to review the Reality PMA. Dr. Yin at that meeting recognized that the Panel recommendation did not include a request for further Panel review of the data. She stated "... if we are not going to have another meeting, we should hear all your (the Advisory Panel) advice now." See Transcript at page 354.

Mr. F. Alan Andersen  
April 10, 1992  
Page 2

We are concerned that further panel review, considered unnecessary by the Panel itself, will delay action on the PMA. If an additional Advisory Panel meeting is convened to review the **Reality** PMA, we believe that it is important that Wisconsin Pharmacal be advised of any FDA concerns that would be discussed at the meeting prior to such a meeting and that sufficient time be allotted at the meeting to permit a full discussion. During such a Panel discussion, Wisconsin Pharmacal and FDA should present a full description of the regulatory history of this product so the scientific data can be placed in context.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

April 14, 1992

Dr. Christine Brauer  
Center for Disease and Radiological Health  
1390 Piccard Drive  
Rockville, MD 20850

Re: Reality™ Device PMA P910064

Dear Dr. Brauer:

I am a consultant currently assisting Wisconsin Pharmacal Company.

One of the projects that I am working on is the water leak test methodology for detecting minute pin-hole leaks in the female condom both as a routine quality control test and as a test to be used for the soon to start post-coital study.

As you know, the design of the female condom is significantly different from the standard male device, specifically at the ring which is at the open end of the device. As a result, if the methodology which was developed for the water leak test for the male device is used to test the female device, an area between the ring and that portion of the device where a twist closure can be obtained is greater than the corresponding area of the male device.

To assure that a comparable area of the female condom is tested by the water leak test a modification of this test is necessary for the female condom. We are therefore recommending that a specially made seal be inserted to tightly close the end of the device at the ring after the appropriate quantity of water has been added sufficient to completely fill the device. The then sealed device would be tested for leaks in accordance with the balance of the approved test methodology.

I have discussed this with Don Marlow who agreed conceptually with the method but felt that your approval was both necessary and important.

Dr. Christine Brauer

April 14, 1992

Page Two

I have a sample of this seal and would be pleased to meet with you to show it to you if you feel that such a meeting is necessary or desirable before you comment on the use of this test modification. We would therefore appreciate it if you could advise us with your advice as soon as possible so that we can implement this modification.

Should you have any questions, please call me at telephone number 919-261-4158 or Fax 919-261-2926.

Sincerely,

*John J. Shea/nbh*

John J. Sea

JJS/nbh

cc: Dr. M.A. Leeper - WPC



QUALITY ♦ INNOVATION

April 14, 1992

VIA FAX (301/427-1977) AND FEDERAL EXPRESS

Christine Brauer, Ph.D.  
Center for Devices and Radiological Health (HFZ-401)  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Dear Dr. Brauer:

Re: Reality Vaginal Pouch (Female Condom) PMA-P910064

This confirms that Dr. John Shea is a consultant for the Wisconsin Pharmacal Company. In this regard, he is requesting counsel from you and your staff regarding specific questions FDA has raised in its letters to Wisconsin Pharmacal regarding the manufacture and quality control aspects of the Reality PMA.

I would appreciate your responding to his queries as they may arrive throughout this process. He is acting on the behalf of Wisconsin Pharmacal and myself.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



June 23, 1992

Philip J. Phillips  
Director, Program Operations Staff  
Office of Device Evaluation  
c/o PMA Document Mail Center (HFZ-401)  
Center for Devices & Radiological Health  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Subject: PMA Supplement-003 to P910064; *Reality* Vaginal Pouch

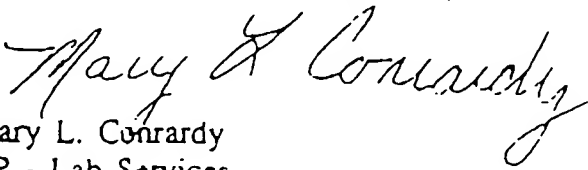
Dear Mr. Phillips:

Wisconsin Pharmacal is submitting this amendment to its PMA application [P910064; *Reality* Vaginal Pouch] to provide additional information requested by the FDA in a Manufacturing Section Deficiency Letter dated December 24, 1991.

As you will note, we have initiated or updated many Standard Operating Procedures. This was done in anticipation of approval for the manufacturing of a Class III device.

Sincerely,

WISCONSIN PHARMACAL CO., INC.

  
Mary L. Conrardy  
VP - Lab Services

mlc/sjp

Enclosure

FDA QUESTIONS - DECEMBER 24, 1991  
WPC RESPONSES - JUNE 23, 1992

Table of Contents

This document is in two volumes. Volume #1 contains Questions 1 - 13. Volume #2 contains Questions 14 - 23. There is an index of questions following the Table of Contents.

VOLUME #1:

Question No. 1 and Answer	GMP - Training
Attachment 1A -	Personnel Qualification and Training (QA-003)
Attachment 1B -	GMP . . . An Overview
Attachment 1C -	Example of Wisconsin Pharmacal Training Material
Attachment 1D -	Training Record
Question No. 2 and Answer	Quality Assurance Monitoring
Attachment 2A -	Quality Systems Audit (QA-005)
Question No. 3 and Answer	Particulate Monitoring
Attachment 3A -	Device Manufacturing Room Environmental Monitoring (QA-010)
Attachment 3B -	Procedure for Viable Particulates Monitoring (ME-405)
Question No. 4 and Answer	Contamination Control Procedure
Attachment 4A -	Cleaning and Sanitation (MFG-001)
Attachment 4B -	Cleaning Procedure for Device Room and Schedule
Attachment 4C -	Disposition of Regulated Waste Materials (QA-026)



# Wisconsin Pharmacal Company

U A L I T Y   ♦   I N N O V A T I O N

July 30, 1992

→ date: 7/31

Amend. 004

revised pages

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Dear Dr. Yin:

Re: Reality Vaginal Pouch  
(PMA P910064)

Enclosed are six (6) sets of the Reality Vaginal Pouch PMA Amendment 004.  
An additional 19 sets are being shipped to you tomorrow (7/31).

This responds to FDA's letter to Wisconsin Pharmacal dated March 26, 1992.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

cc F. Alan Andersen (Letter Only, Fax)  
Amanda Pederson (Letter Only, Fax)

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2008  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

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1355-7738-3

Date

7/30/92

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Dr. Mary Ann Leeper

Company Wisconsin Pharmacal

PHARMENIX HEALTH CARE INC

Street Address

910 N MICHIGAN AVE STE 220A

City

CHICAGO

State

IL

ZIP Required

60611

Your Phone Number (Very Important)

(312) 280-2282

Department/Floor No.

To (Recipient's Name) Please Print

Dr. Lillian Yin

Company c/o IDS Document Mail Center (EXPRESS) No.

Center for Devices and Radiological Health

Food &amp; Drug Administration

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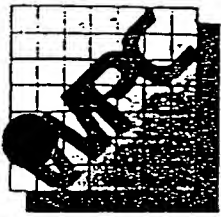
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<b>5</b> DELIVERY AND SPECIAL HANDLING (Check services required) 1 <input type="checkbox"/> HOLD FOR PICK-UP (see box 19) 2 <input type="checkbox"/> DELIVER SATURDAY (same charge as business day) 3 <input type="checkbox"/> DELIVER WEDNESDAY (same charge as business day) 4 <input type="checkbox"/> DANGEROUS GOODS (same charge as business day) 5 <input type="checkbox"/> DRY ICE (same charge as business day) 6 <input type="checkbox"/> OTHER SPECIAL SERVICE (same charge as business day) 7 <input type="checkbox"/> SATURDAY PICK-UP (same charge as business day) 8 <input type="checkbox"/> HOLIDAY DELIVERY (same charge as business day)		<b>6</b> DIMENSIONAL WEIGHT (Chargeable Weight) L X W X H 10 10 10 11 11 11 12 12 12 13 13 13 14 14 14 15 15 15 16 16 16 17 17 17 18 18 18 19 19 19 20 20 20 21 21 21 22 22 22 23 23 23 24 24 24 25 25 25 26 26 26 27 27 27 28 28 28 29 29 29 30 30 30 31 31 31 32 32 32 33 33 33 34 34 34 35 35 35 36 36 36 37 37 37 38 38 38 39 39 39 40 40 40 41 41 41 42 42 42 43 43 43 44 44 44 45 45 45 46 46 46 47 47 47 48 48 48 49 49 49 50 50 50 51 51 51 52 52 52 53 53 53 54 54 54 55 55 55 56 56 56 57 57 57 58 58 58 59 59 59 60 60 60 61 61 61 62 62 62 63 63 63 64 64 64 65 65 65 66 66 66 67 67 67 68 68 68 69 69 69 70 70 70 71 71 71 72 72 72 73 73 73 74 74 74 75 75 75 76 76 76 77 77 77 78 78 78 79 79 79 80 80 80 81 81 81 82 82 82 83 83 83 84 84 84 85 85 85 86 86 86 87 87 87 88 88 88 89 89 89 90 90 90 91 91 91 92 92 92 93 93 93 94 94 94 95 95 95 96 96 96 97 97 97 98 98 98 99 99 99 100 100 100	
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**Wisconsin  
Pharmacal  
Company**

QUALITY ♦ INNOVATION

11/10/11

FDA date: 8/3/11

~~Final Registration study Report~~

19 sets of

004 -

Responses to FDA 3/12

11/10/11

See attached

FDA date: 8/3

Final Rep'n bear study Report



# Wisconsin Pharmacal Company

QUALITY ♦ INNOVATION

→ date: 7/31

inval. 004

July 30, 1992

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Dear Dr. Yin:

Re: Reality Vaginal Pouch  
(PMA P910064)

Enclosed are six (6) sets of the Reality Vaginal Pouch PMA Amendment 004.  
An additional 19 sets are being shipped to you tomorrow (7/31).

This responds to FDA's letter to Wisconsin Pharmacal dated March 26, 1992.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

cc F. Alan Andersen (Letter Only, Fax)  
Amanda Peterson (Letter Only, Fax)

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2008  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

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Date  
7/31/92

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**Dr. Mary Ann Leeper**

Company  
**PHILIPPIAN HEALTH CARE INC**

Street Address  
**919 N MICHIGAN AVE STE 2204**

City  
**CHICAGO**

State  
**IL**

Zip Required  
**60611**

Your Phone Number (Very Important)  
**(312) 280-2284**

Department/Floor No.  
**60611**

Recipient's Name (Please Print)  
**Dr. Lillian Yin**

Company  
**e/o THE Document Mail Center-HERPES No. Center for Devices and Radiological Health**

Exact Street Address (No P.O. Boxes or R.D. Zip Code)  
**Food & Drug Administration  
1390 Piccard**

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**Rockville, Maryland**

State  
**MD**

Zip Required  
**20850**

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28 ☐ FEDEX TUBE  
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# FAMILY HEALTH INTERNATIONAL

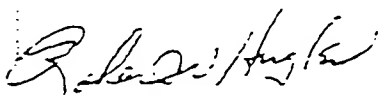
September 24, 1992

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development  
Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

Dear Dr. Leeper:

This letter authorizes the Food and Drug Administration to include by reference information in Family Health International's device master file (MAF-421) for review of PMA P910064 (Reality Vaginal Pouch). Specifically, the information in this MAF contains a detailed report on the completed *Phase II Evaluation of the Contraceptive Efficacy and Clinical Acceptability of a Female Condom*, and ASCII and SAS datasets for the clinical data summarized in this report. Results from the completed study as well as the ASCII dataset were specifically requested by the FDA in their March 26, 1992 letter to Wisconsin Pharmacal.

Sincerely yours,



Robert W. Hughes  
Vice President  
Administration



# Wisconsin Pharmacal Company

QUALITY ♦ INNOVATION

9/28/92

September 25, 1992

VIA FAX (301) 427-1977 AND FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Re: Reality Vaginal Pouch, PMA P910064

Dear Dr. Yin:

Herewith is the letter which authorizes the FDA to reference the Family Health International Device Master File (MAF-421) as part of the review of Wisconsin Pharmacal's PMA, P910064, on the Reality Vaginal Pouch.

I am sending this letter by fax today and Federal Express so that you will realize that Wisconsin Pharmacal has received permission to cross reference the data. The original letter will be sent to you by Federal Express on Monday, September 28, once I receive it here from Family Health International (due to Wisconsin Pharmacal Monday morning).

FDA will receive 25 copies of the clinical study report on Monday morning, Federal Expressed directly to you from Family Health International, per Colin Pollard's request. The MAF contains the detailed report, as well as the ASCII and SAS datasets.

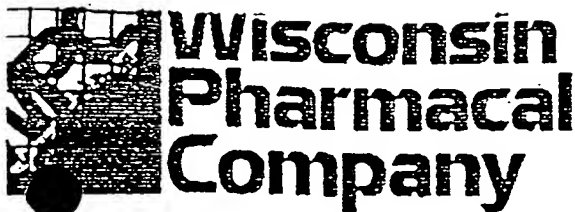
Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

Enclosure

cc: F. Alan Andersen, Ph.D. (Via Fax 301/427-1022 and Federal Express)  
Ms. Amanda B. Pedersen (Via Fax 301/443-1306 and Federal Express)

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541, Fax: (312) 280-9360



ALITY ♦ INNOVATION

September 28, 1992

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Re: Reality Vaginal Pouch PMA P910064

Dear Dr. Yin:

Enclosed is the original copy of the cross-reference letter authorizing FDA to reference Family Health International's MAF-421 as part of its review of the PMA, P910064.

Sincerely,

Mary Ann Loeper, Ph.D.  
Senior Vice President of Development

Enclosure

cc: F. Alan Andersen, Ph.D. (Via Fax 301/427-1977)  
Ms. Amanda B. Pedersen (Via Fax 301/227-6807)

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541, Fax: (312) 280-9360

REALITY - PMA P210064  
INDEX OF TOPICS

<u>Topics</u>	<u>Question #</u>
Acceptability	2
Adverse Effects	2, 22
Allergy	2
Bacteriophage Studies	13, 14, 15, 16, 17
Carcinogenicity	8
Comparability	2, 22
Contraceptive Efficacy	2, 22
Directions for Use	2, 24, 25
Discontinuation Rates	2, 22
Dislodgement	2, 23
Dulbecco's Buffer	18
Dyspareunia	2
Efficacy	2, 22
Ex-U.S. Studies	2
Helium Leak	20
Instructions for Use	2, 24, 25
Irritation, Vaginal	2, 6
Labeling	2, 24, 25
Latex Phage Study	15
Lubricant, Oil Based	4
Lubricant, Water Based	3
Marketing History	1
MDA	7
Method Failure	2, 22
Outer Ring Bonding	11
Permeability	2, 13, 14, 15, 16, 17
Phase I Studies	2
Physical Properties	9
Pregnancy Use-Effectiveness	22
Pressure Profile, Phage Study	16
Ring Supplier	5
Rip/Tear Repeat Study	2, 23
Risk Analysis	21
Safety	2, 22
Seam Strength	10
Shelf Life	12
Spiking	13
Stability	2
Technical Revisions	2
Toxicity	2
Trichomonas Reinfection	2
Tween 80	13
User Failure	2, 22
Vaginal Trauma	2
Water Leak Test	19

Note: Question # 1 is a summary of the technical studies completed

## REALITY

### RESPONSES TO FDA QUESTIONS; MARCH 1992

#### TABLE OF CONTENTS

The responses and appendices are in 4 volumes. The contents of each volume are listed below, followed by an Index of Topics.

#### Volume 1: Responses to Questions # 1 through 12

Q and A #	1	Summary of Safety and Effectiveness
	2	Revised, Updated Technical Section
	3	Water-Based Secondary Lubricant
	4	Oil-Based Secondary Lubricant
	5	Ring Supplier
	6	Long-Term Vaginal Irritation (full reports in Volume 4)
	7	MDA Analysis
	8	Carcinogenicity Risk Assessment
	9	Physical Properties of Final Product
	10	Seam Strength
	11	Bonding of Outer Ring
	12	Shelf-Life; Real Time Studies

#### Volume 2: Responses to Questions # 13 - 25

Q and A #	13	Bacteriophage Studies: Tween 80; Testing Component Interaction; Spiking
	14	Bacteriophage: Reassay Data
	15	Bacteriophage: Latex Condoms
	16	Bacteriophage: Pressure Profile
	17	Bacteriophage: Sensitivity of Method
	18	Bacteriophage: Dulbecco's Buffer
	19	Water-Leak Test
	20	In-Line Helium Gas Leak Test
	21	Phase I Risk Analysis
	22	Contraceptive Effectiveness Study
	23	Repeat Rip/Tear Study
	24	Rewrite of Product Labeling
	25	Product Labeling: Directions for Use

Volume 3: Appendices to Questions # 1 and 2

- |   |   |   |
|---|---|---|
| # | 1 | Bibliography  |
|   | 2 | USP Class VI Plastic Report   |
|   |   | Ex-U.S. Studies   |
|   |   | <ul style="list-style-type: none"><li>• Dynamic Study Using Ultrasound</li><li>• Ultrasound of Human Coitus</li><li>• Allergy Study</li><li>• Dyspareunia Study</li><li>• Use-Effectiveness and Acceptability</li><li>• Use-Acceptability</li><li>• Permeability - Herpes Simplex I</li></ul> |

Volume 4: Appendices to Questions # 3, 6, and 23

- |   |    |  |
|---|----|--|
| # | 3  | CTFA Listing for Ingredients   |
|   |    | CTFA Safety Assessment   |
|   |    | Scientific Studies - Diazolidinyl  |
|   |    | Material Formula - Water Base Lubricant  |
|   | 6  | Final Reports: Toxicity  |
|   |    | <ul style="list-style-type: none"><li>• Vaginal Irritation Studies</li><li>• Ex-U.S. Study, Cytotoxicity</li><li>• Ex-U.S. Study, Vaginal Irritation, Rabbit</li></ul> |
|   | 23 | Repeat Rip/Tear Study  |
|   |    | <ul style="list-style-type: none"><li>• Summary</li><li>• RTL Segment Report</li><li>• Tektagen Segment - Report</li></ul>   |



October 29, 1992

VIA FEDERAL EXPRESS AND FAX (301/427-1977)

F. Alan Andersen, Ph.D., Acting Director  
Office for Device Evaluation  
U.S. Food & Drug Administration  
1390 Piccard Drive, HFZ-400  
Rockville, Maryland 20850

Re: PMA 910064, Reality Vaginal Pouch

Dear Dr. Andersen:

I am writing to thank you and others at ODE for meeting with us on October 26 to discuss the **Reality** PMA. The ability to discuss the reviewers' concerns provided greater clarity as to what additional information is needed. We understand from your comments that not all concerns are of equal weight but that they need to be addressed and resolved prior to an agency decision. To the extent possible, we intend to respond to the concerns raised at the meeting by November 16, 1992. Some issues, such as preclinical sensitivity studies with the secondary lubricant, cannot be completed by November 16, but we will have work underway.

Since our meeting, I have talked to Mr. Pollard who has confirmed that there will be a December 10, 1992 Panel meeting assuming a suitable location can be found. Based on our meeting, we anticipate that the principal discussion points will revolve around the data handling, interpretation and adequacy of the use-effectiveness study, and labeling. We are preparing accordingly. Mr. Pollard agreed to forward to us FDA's questions for the Panel as soon as they are prepared, hopefully 10 to 14 days prior to the December 10 meeting. If FDA intends to present its proposed labeling, or revisions of labeling submitted by WPC to the Advisory Panel, we would appreciate receiving copies at the same time as the Panel members so that we can be prepared to discuss FDA's proposals. If FDA intends to submit its analyses of submitted information to the Panel, we would appreciate receiving that information. It is our objective to be as responsive to FDA issues as possible so that the Panel meeting can be constructive.

Dr. F. Alan Andersen

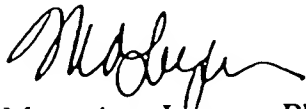
October 29, 1992

Page 2

With regard to our forthcoming November 16, 1992 submission, I will coordinate with Mr. Pollard to ensure that the submission will be ready for transmittal to Panel members.

Again, we appreciate your courtesy at the meeting and ask that you consider our requests for copies of any information prepared by FDA that is provided to Advisory Panel members.

Sincerely,



Mary Ann Leeper, Ph.D.

Senior Vice President of Development

CC: Ms. Amanda B. Pedersen (Federal Express and Fax 301/227-6807)

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax (312) 280-9360

004

REALITY - PMA P910064  
INDEX OF TOPICS

~~10/30~~  
~~PD# 10/30~~  
~~004~~

<u>Topics</u>	<u>Question #</u>
Acceptability	2
Adverse Effects	2, 22
Allergy	2
Bacteriophage Studies	13, 14, 15, 16, 17
Carcinogenicity	8
Comparability	2, 22
Contraceptive Efficacy	2, 22
Directions for Use	2, 24, 25
Discontinuation Rates	2, 22
Dislodgement	2, 23
Dulbecco's Buffer	18
Dyspareunia	2
Efficacy	2, 22
Ex-U.S. Studies	2
Helium Leak	20
Instructions for Use	2, 24, 25
Irritation, Vaginal	2, 6
Labeling	2, 24, 25
Latex Phage Study	15
Lubricant, Oil Based	4
Lubricant, Water Based	3
Marketing History	1
MDA	7
Method Failure	2, 22
Outer Ring Bonding	11
Permeability	2, 13, 14, 15, 16, 17
Phase I Studies	2
Physical Properties	9
Pregnancy Use-Effectiveness	22
Pressure Profile, Phage Study	16
Ring Supplier	5
Rip/Tear Repeat Study	2, 23
Risk Analysis	21
Safety	2, 22
Seam Strength	10
Shelf Life	12
Spiking	13
Stability	2
Technical Revisions	2
Toxicity	2
Trichomonas Reinfection	2
Tween 80	13
User Failure	2, 22
Vaginal Trauma	2
Water Leak Test	19

Note: Question # 1 is a summary of the technical studies completed

10/20

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REALITY

RESPONSES TO FDA QUESTIONS; MARCH 1992

TABLE OF CONTENTS

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Volume 1: Responses to Questions # 1 through 12

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	8	Carcinogenicity Risk Assessment
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	10	Seam Strength
	11	Bonding of Outer Ring
	12	Shelf-Life; Real Time Studies

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	16	Bacteriophage: Pressure Profile
	17	Bacteriophage: Sensitivity of Method
	18	Bacteriophage: Dulbecco's Buffer
	19	Water-Leak Test
	20	In-Line Helium Gas Leak Test
	21	Phase I Risk Analysis
	22	Contraceptive Effectiveness Study
	23	Repeat Rip/Tear Study
	24	Rewrite of Product Labeling
	25	Product Labeling: Directions for Use

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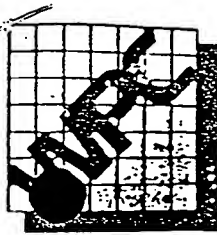
10/20

Volume 3: Appendices to Questions # 1 and 2

- |   |   |   |
|---|---|---|
| # | 1 | Bibliography  |
|   | 2 | USP Class VI Plastic Report   |
|   |   | Ex-U.S. Studies   |
|   |   | <ul style="list-style-type: none"><li>• Dynamic Study Using Ultrasound</li><li>• Ultrasound of Human Coitus</li><li>• Allergy Study</li><li>• Dyspareunia Study</li><li>• Use-Effectiveness and Acceptability</li><li>• Use-Acceptability</li><li>• Permeability - Herpes Simplex I</li></ul> |

Volume 4: Appendices to Questions # 3, 6, and 23

- |   |    |  |
|---|----|--|
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|   |    | CTFA Safety Assessment   |
|   |    | Scientific Studies - Diazolidinyl  |
|   |    | Material Formula - Water Base Lubricant  |
|   | 6  | Final Reports: Toxicity  |
|   |    | <ul style="list-style-type: none"><li>• Vaginal Irritation Studies</li><li>• Ex-U.S. Study, Cytotoxicity</li><li>• Ex-U.S. Study, Vaginal Irritation, Rabbit</li></ul> |
|   | 23 | Repeat Rip/Tear Study  |
|   |    | <ul style="list-style-type: none"><li>• Summary</li><li>• RTL Segment Report</li><li>• Tektagen Segment - Report</li></ul>   |



**Wisconsin  
Pharmacal  
Company**

Q U A L I T Y   ♦   I N N O V A T I O N

11/16/92  
Amend 005

November 13, 1992

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Re: Reality Vaginal Pouch, PMA P910064, Amend005

Dear Dr. Yin:

Enclosed are 25 copies of Wisconsin Pharmacal's responses to questions raised by FDA regarding the July, 1992 Submission (P910064-004), including questions related to the Contraceptive Efficacy Study. I understand you will make this submission available to the Panel as soon as possible.

This submission is to respond to the questions raised by FDA in October. Please note we have not attempted to restate the information submitted to FDA in July, 1992 or the earlier PMA of October, 1991. However, the responses that follow need to be read in the context of the prior submissions, particularly July, 1992.

In an attempt to facilitate a review and also for general reference, we have included as Appendix 1 (Volume 2) the summary of all the **Reality** studies and results as submitted to FDA in response to Question # 2 in July.

Based on our discussion, we recognize that some of the information has higher priority, particularly in preparation for the December 10-11 Panel Meeting. We believe the critical areas for discussion at the Panel Meeting are the (1) dual claims of contraception and STD prevention, (2) the adequacy of the Contraceptive Efficacy Study, and (3) the specific information included in the labeling. Given this focus, we have addressed these issues in Sections A and B based on our interpretation of FDA's concerns. The rest of the sections include information to address more precisely specific questions raised by FDA based on its review of the July submission.

Dr. Lillian Yin  
November 13, 1992  
Page 2

The following is an outline of the areas covered: Clinical (A); Labeling (B);  $\phi$ X174 (C); Physical Properties (D); Chemistry (E); Quality Assurance (F); and Toxicity (G).

We now await receipt of the formal questions which FDA will pose to the Advisory Panel on December 10 and 11. Colin Pollard said he would fax a draft to me as soon as it was available. He said it would be about 10-14 days prior to the meeting.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

cc: Dr. F. A. Andersen (letter only)  
Ms. Amanda B. Pedersen (letter only)

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541, Fax: (312) 280-9360



December 1, 1992

VIA FAX (301/427-1977)

F. Alan Andersen, Ph.D., Acting Director  
Office for Device Evaluation  
U.S. Food & Drug Administration  
1390 Piccard Drive, HFZ-400  
Rockville, Maryland 20850

Re: PMA 910064, Reality Vaginal Pouch

Dear Dr. Andersen:

This is to confirm that FDA received today a package of technical information requested by Don Marlowe during our October 26 discussions regarding data related to the validation of the **Reality** manufacturing process. At that time, we agreed to have this information to FDA by December 1.

I spoke with Colin Pollard this morning. He advised that Dr. Yin and others will be calling me on Thursday morning with the Panel questions for next week's meeting. Needless to say, I am anxiously looking forward to the Panel sessions.

Thank you again for your assistance and for Amanda Pedersen's help in bringing resolution to this process.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

CC: Ms. Amanda B. Pedersen (Via Fax 301/227-6807)  
Dr. Lillian Yin (Via Fax 301/427-1287)

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



12/4/92

December 3, 1992

VIA FEDERAL EXPRESS

Mr. Colin Pollard  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 28050

Dear Colin:

Re: Reality Vaginal Pouch (WPC-333)

The following addresses the points we discussed this morning about the up and coming Panel hearing:

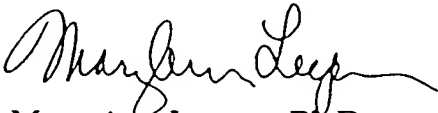
1. WPC will use two hours to make a presentation to the Panel. At this time, I am not able to give you names of presenters in addition to myself because, in just having received the questions, we need another day to talk with our consultants and to finalize the approach. I will send you by fax the names of the speakers, approximate times, and associations on Monday morning, December 7.
2. We will require an overhead for our A-V needs.
3. Enclosed are an extra 25 copies of the proposed labeling submitted to you in November. Also enclosed for your use is a hard copy of the proposed labeling and a disk which is WP5.1.
4. Enclosed is a disk in WP5.1 of the responses to Question No. 1, Summary of Safety and Efficacy, and No. 2, Revised Updated Technical Section, submitted to you in July.
5. Chris Brauer asked what the symbols "osi" refer to on Page 4 of Section F of the November 16 submission. It means the following: "ounces per square inch" (instead of pounds per square inch).

Mr. Colin Pollard  
December 3, 1992  
Page 2

6. On re-reading the draft questions, I suggest you revise Question #4. a 1. to "22% failure for Latin American women." The U.S. group had Hispanic women as well as women of color in the demographics.

If you have any questions regarding the enclosed, please call me immediately; otherwise I will talk with you on Monday with the final information of our presenters.

Sincerely,

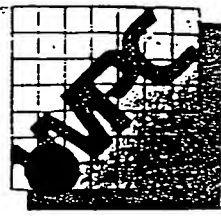


Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosures

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
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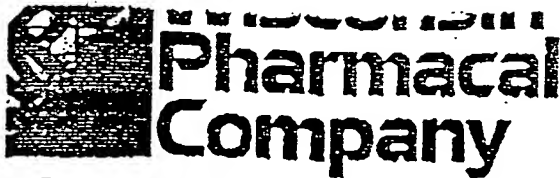


**Wisconsin  
Pharmacal  
Company**

QUALITY ♦ INNOVATION

FDA date: 12/7

*Agendas for the 12/10 meeting*



December 4, 1992

VIA FAX (301/427-1977)

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Re: Reality Vaginal Pouch, PMA P910064

Dear Dr. Yin:

This confirms our telephone conversation.

Wisconsin Pharmacal agrees that FDA can discuss the clinical results of the Contraceptive Efficacy Study in meetings it has scheduled the week of 12/7/92 with the National Women's Health Network providing the data and analysis discussed are FHI's reported data, not FDA's analysis of the data; e.g., FHI's life-table calculations, not FDA's calculations.

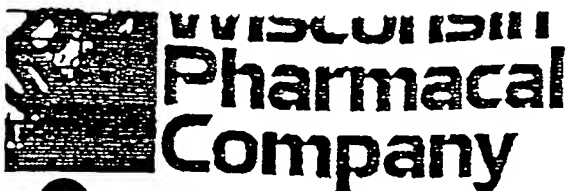
Sincerely,

A handwritten signature in cursive script, appearing to read "Mary Ann Leeper".

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



A T Y ♦ I N N O V A T I O N

December 4, 1992

VIA FEDERAL EXPRESS

Mr. Colin Pollard  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Dear Colin:

Re: Reality Vaginal Pouch (WPC-333)

Per your request, enclosed are 15 Reality demonstrator devices. Please note they are not prelubricated nor quality released. They are for demonstration purposes only.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosures

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
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**Wisconsin  
Pharmacal  
Company**

ACTIVITY ♦ INNOVATION

FDA date: 12/7

*Agendas for the 12/10 meeting*



# Wisconsin Pharmacal Company

Q U A L I T Y   ♦   I N N O V A T I O N

December 7, 1992

VIA FAX (301/427-1987)

Mr. Colin Pollard  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard (HFZ-401)  
Rockville, Maryland 20850

Dear Colin:

Re: Reality Vaginal Pouch (WPC-333)

Listed below are the names and titles of those who will be making the presentation during the two-hour time frame on Thursday morning on behalf of Wisconsin Pharmacal:

- Mary Ann Leeper, Ph.D., Vice President Development, Wisconsin Pharmacal (WPC).
- Malcom Potts, M.D., on his behalf, not a consultant to Wisconsin Pharmacal.
- Ms. Rosalie Dominik, Senior Statistician (not a consultant to WPC).
- James Trussell, Professor of Economics and Public Affairs and Director Office of Population Research and Associate Dean, Woodrow Wilson School of Public and International Affairs, Princeton University, consultant to WPC.
- Felicia H. Stewart, M.D., Clinical Investigator, Valley Center for Women's Health (consultant to WPC).
- David Soper, M.D., Clinical Investigator, Medical College of Virginia Hospitals (consultant to WPC).

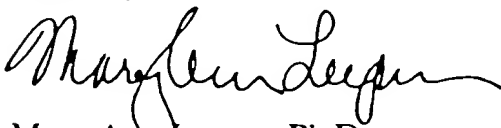
Mr. Colin Pollard  
December 7, 1992  
Page 2

- Denise O. Shervington, M.D., Assistant Professor of Psychiatry, LSU Medical Center, studied labeling instructions for use and for WPC.
- Mervyn Silverman, M.D., President, American Foundation for AIDS Research (consultant to WPC).

Please note that, in addition to an overhead projector, we will need a microphone at the overhead which can be worn either on the lapel or around the neck.

Will you please fax me the final questions to the Panel as soon as they are available.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



12/16/92

December 14, 1992

VIA FEDERAL EXPRESS AND FAX (301) 427-1987 or 427-1977

Mr. Colin Pollard  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Dear Colin:

Re: Reality Vaginal Pouch (WPC-333)  
PMA P910064

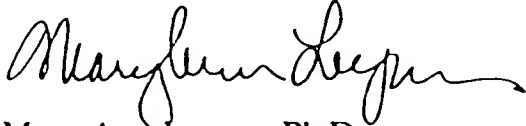
Following up your request, enclosed is a Xerox of the actual slide that Sheryl Ruzek used to write the proposed labeling and which was shown to the Panel and approved by the Panel for the labeling at the Thursday, December 10 session. I have also had it typed for your convenience.

I noted that the wording that was used in the *TALK* paper is different from what was finally outlined by the Panel. You'll remember that the wording used in the *TALK* paper was discussed prior to the Panel wording on the enclosed. My assumption is I will be hearing from you soon regarding next steps.

Mr. Colin Pollard  
December 14, 1992  
Page 2

It was quite a session the other day. Needless to say, we are all still reeling from it as I am sure you all are. Everybody worked very hard from the FDA as well as Wisconsin Pharmacal and the various consultants.

Sincerely,

A handwritten signature in cursive script, appearing to read "Mary Ann Leeper".

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

CC: F. Alan Andersen, Ph.D.  
Lillian Yin, Ph.D.

MAL/dlp

Enclosures

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

## ABOUT REALITY'S EFFECTIVENESS

(1) Effectiveness - Because Reality is the first vaginal pouch approved for marketing, special attention has been given to accelerate its availability. Reality has not been as widely tested as the contraceptive sponge, cervical cap, or diaphragm. However, several studies show that the risk of becoming pregnant

when Reality is used is about the same as when other barrier devices are used. ~~The actual rate of pregnancy may be different~~

The pregnancy failure rate, after 6 months of use, among U.S. and Latin American women who participated in the study, was 14.9%. For U.S. women alone the failure rate was 12.2%.

Among U.S. women who used Reality as the directions show, with every sex act, the failure\* rate was 5.4%.

Pregnancy failure rates among U.S. women based on 6 months use/100 women:

	6 Month Failure Rate	6 Month Perfect* Use Failures
Reality	12.2 %	5.4 %
Contraceptive Sponge	11.7 %	8.5-8.8 %
Cervical Cap	10.9 %	4.3-5.8 %
Diaphragm	8.7 %	1.7-4.7 %
Male Condom	?	?

~~Failure rate for male condoms has not been studied like~~

~~Reality, the Sponge, Cap or Diaphragm. Review of the literature for failure rates suggests a 2 month failure rate of 1.5% (Roe 1)~~

In the limited research done thus far,

which used in the general population

The pregnancy rate for 12 months of use can be estimated by multiplying these rates by 1.5 to 2.

## ABOUT REALITY'S EFFECTIVENESS

- (1) **Effectiveness** - Because Reality is the first female condom approved for marketing, special attention has been given to accelerate its availability. Reality has not been as widely tested as the contraceptive sponge, cervical cap, or diaphragm. In the limited research done thus far, the risk of becoming pregnant when Reality is used presented is below. The actual rate of pregnancy may be different when used in the general population.

The pregnancy failure rate, after 6 months of use, among U.S. and Latin American women who participated in the study, was 15.1%. For U.S. women alone the failure rate was 12.3%.

Among U.S. women who used Reality as the directions show, with every sex act, the failure\* rate was 5.4%.

Pregnancy failure rates among U.S. women based on 6 months use/100 women:

	6-Month Failure Rate	6-Month Perfect* Use Failures
Reality	12.3%	5.4%
Contraceptive Sponge	11.7%	8.5-8.8%
Cervical Cap	10.9%	4.3-5.8%
Diaphragm	8.7%	1.7-4.7%
Male Condom	?	?

The pregnancy rate for 12 months of use can be estimated by multiplying these rates by 1.5 to 2.



December 17, 1992

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Re: Reality Vaginal Pouch, PMA P910064

Dear Dr. Yin:

Enclosed for your files is a copy of James Trussell's final paper regarding the contraceptive efficacy of Reality, including his new analyses on HIV reduction presented to the Panel December 10.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosure

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

## Contraceptive Efficacy of the Reality Female Condom: Comparison with Other Barrier Methods

The Reality female condom was developed by Wisconsin Pharmacal Company to provide women with a female-controlled barrier device effective at preventing both pregnancy and transmission of STDs, including HIV. Currently, the only device that is approved for both purposes is the latex condom worn by, and therefore controlled by, the male.

In order to test the contraceptive efficacy of the new device, Family Health International (FHI) and the Contraceptive Research and Development Program (CONRAD) conducted a clinical trial in nine centers, six in the United States and three in Latin America. Altogether, 348 women entered the six-month trial.

The final audited data show that the 6-month life-table failure rate for the Reality female condom is  $15.1\% \pm 2.3\%$ . As shown in Table 1, failure rates are lower among women in the United States ( $12.3\% \pm 2.5\%$ ) than among women in Latin America ( $22.0\% \pm 4.8\%$ ), although the difference is not statistically significant.<sup>1</sup> How do these failure rates compare with those for other barrier methods of contraception?

### Comparison of the Reality Female Condom with Male Condoms

Because the Reality female condom is intended to be used for protection against both accidental pregnancy and STD transmission, the most natural efficacy comparison would be with the male condom. Results concerning the contraceptive efficacy of the male condom are shown in Table 2, which is updated from earlier versions published by Trussell and Kost [1987] and Hatcher *et al.* [1990]. Unfortunately, a careful reading of these studies reveals that their results cannot be meaningfully compared with those for the Reality condom.

Of the 13 studies in Table 2, eight [Peel 1972; Jones and Forrest 1992a; Bracher and Santow 1992; Schirm *et al.* 1982; Grady *et al.* 1983; Vaughan *et al.* 1977; Grady *et al.* 1986; Westoff *et al.* 1961] are based on retrospective reports of women in sample surveys; results from these population-based surveys are simply not comparable with results from a carefully controlled prospective clinical trial such as that used to evaluate the Reality female condom.

<sup>1</sup> All statistical tests reported below are z-tests of differences in proportions, where the proportions are the life-table probabilities of experiencing an accidental pregnancy within 6 months. The tests are two-sided; the significance level is 5%.

because the research designs are so different. John [1973] surveyed three groups in Shepshead, England — (1) a random sample of married women in the town's only clinical practice, (2) all women who attended the family planning clinic in the town during a one-year period, and (3) all women in the town whose pregnancy ended in a birth or an induced abortion during that year — to obtain their retrospective reports of contraceptive experience. Potts and McDevitt [1975] assessed the efficacy of spermicidally-lubricated condoms by recruiting a sample of condom users from the regular mail-order customers at the Marie Stokes Memorial Centre. Prospective male participants were asked to use the new condom exclusively for a period of two years. The results are somewhat difficult to interpret because 77% of the males were aged 40 or over and so might be expected to have low coital frequency. Moreover, the product contained a spermicide, whereas the Reality condom is not spermicidally lubricated.

The remaining three studies are all based on the same prospective clinical trial (the Oxford/FPA study), but results from these studies are still not comparable to those for Reality. At recruitment, all women were required to be married and aged 25-39 and to have been using the diaphragm, pill, or IUD successfully for at least five months. The last criterion ensures that the sample is self-selected for better than average contraceptive use or lower than average fecundity or coital frequency. Combined with the age criterion, the sample of eventual condom users would be expected also to have lower than average coital frequency.

Even on the differences in research design, comparisons between the contraceptive efficacies of the Reality female condom and male condoms cannot be made with any confidence. Nevertheless, since the 6-month life-table failure rate for Reality (15.1% among all women and 12.3% among women in the United States) generally exceeds the 12-month life-table failure rates for male condoms that are not spermicidally lubricated, it is tempting to conclude that Reality is somewhat less effective at preventing pregnancy but that the difference is not large. There is, however, one important additional reason for thinking that the contraceptive efficacies of the male and female condoms are more similar than a mechanical comparison of failure rates would indicate. Failure rates for the male condom based on survey data are known to be too low because induced abortions are not fully reported in the surveys [Jones and Forrest 1992b]. When Jones and Forrest [1992a] add estimated contraceptive failures that were not reported in the 1988 National Survey of Family Growth (NSFG), the 12-month failure rate for the condom is approximately doubled (from 7.2% to 14.8%). In the Reality trial, not only were induced abortions recorded, but also pregnancies were counted if they were chemically confirmed even if they resulted in spontaneous abortions before they could be clinically confirmed. In contrast, only clinically confirmed pregnancies have been counted in the male condom studies.

## Comparison of the Reality Female Condom with the Diaphragm, Sponge, and Cervical Cap

How does the contraceptive efficacy of Reality compare with that of the diaphragm, sponge, and cervical cap? Data on the relative efficacy of the diaphragm, sponge, and cervical cap during typical use are exceptionally good because they come from two clinical trials conducted in the United States in which participating women were randomly assigned to use either the sponge or the diaphragm [FHI 1985] or to use either the cervical cap or the diaphragm [Bernstein 1986]. Data from the Reality trial should be comparable to data from these two prospective trials, with three important caveats, all of which, *ceteris paribus*, would make failure rates for Reality higher. First, the sponge-diaphragm and cap-diaphragm trials counted only clinically confirmed pregnancies. In contrast, pregnancy tests were given to women in the Reality trial at their time of exit and two weeks later, and pregnancies were counted if they were chemically confirmed. Second, the Reality protocols called for exclusion of women whose usual coital frequency was fewer than eight times per month and discontinuation of women if their coital frequency fell below four times per month (although not all women whose coital frequency did fall below four times per month were in fact discontinued). Third, the sponge-diaphragm and cap-diaphragm trials seem to have been less well controlled — as evidenced by 6-month loss to follow up (LFU) rates that were considerably higher: 19.1% for the sponge and 23.3% for the diaphragm in the sponge-diaphragm trial, 20.0% for the cervical cap and 24.5% for the diaphragm in the cap-diaphragm trial, *versus* 8.1% for all centers and 8.6% for domestic centers in the Reality trial. All analyses of these data employ the standard assumption that the subsequent experience of those lost to follow up is the same as the experience of those observed. However, LFU rates as high as those observed in the sponge-diaphragm and cap-diaphragm trials inevitably raise concern about the quality of the results. The rare attempt to locate those LFU in order to validate the universal assumption that they became pregnant while using at the same rate as those who remained under observation (and that none were pregnant at the time they were last observed) is sobering. For example, Tietze, Poliakoff, and Rock [1951] found that the Pearl index for calendar rhythm rose from 9.4 to 14.4 as a result of resolution of cases LFU.

Efficacy results from the sponge-diaphragm and cap-diaphragm trials are displayed in Table 3. In the sponge-diaphragm trial, data on 1437 women from 13 clinics in the United States yielded 6-month life-table failure rates of  $11.6\% \pm 1.4\%$  for the sponge ( $n = 720$ ) and  $7.7\% \pm 1.2\%$  for the diaphragm ( $n = 717$ ) [Trussell and Strickler 1992]. Among parous women, the 6-month life-table failure rates were  $19.6\% \pm 3.6\%$  for the sponge ( $n = 181$ ) and  $4.2\% \pm 1.9\%$  for the diaphragm ( $n = 155$ ). Among women with  $\leq 12$  years of education, the 6-month life-table failure rates were  $14.1\% \pm 3.4\%$  for the sponge ( $n = 164$ ) and  $12.5\% \pm 3.2\%$  for the diaphragm ( $n = 170$ ). Among women less than 25 years of age, the 6-month life-table failure rates were  $11.9\% \pm 2.3\%$  for the sponge ( $n = 300$ ) and  $11.1\% \pm 2.1\%$  for

the diaphragm ( $n = 335$ ). In the cap-diaphragm trial, data on 1394 women in Los Angeles, San Diego, and San Francisco yielded 6-month failure rates of  $10.2\% \pm 1.8\%$  for the cervical cap ( $n = 687$ ) and  $8.3\% \pm 1.3\%$  for the diaphragm ( $n = 707$ ) [Trussell and Strickler 1992]. Failure rates among parous women were  $18.0\% \pm 4.5\%$  for the cervical cap ( $n = 117$ ) and  $9.2\% \pm 3.6\%$  for the diaphragm ( $n = 114$ ). Among women with  $\leq 12$  years of education, the 6-month life-table failure rates were  $16.8\% \pm 3.8\%$  for the cervical cap ( $n = 167$ ) and  $13.1\% \pm 3.2\%$  for the diaphragm ( $n = 182$ ). Among women less than 25 years of age, the 6-month life-table failure rates were  $9.9\% \pm 2.1\%$  for the cervical cap ( $n = 310$ ) and  $9.3\% \pm 2.1\%$  for the diaphragm ( $n = 315$ ).

Given that failure rates in these two trials were generally higher for parous women, for less-educated women, and for younger women, it is important to make comparisons with the Reality condom not only for the overall sample but also for subgroups. These comparisons are shown in Table 3 and in Figure 1. Close examination of this table reveals that:

- Although the overall failure rate for Reality for the total sample is higher than the failure rates for the diaphragm, sponge, and cervical cap, it statistically significantly differs only from the failure rate for the diaphragm in both the sponge-diaphragm and the cap-diaphragm trials. It should be noted that in the sponge-diaphragm trial, the failure rate for the sponge is statistically significantly different from the failure rate for the diaphragm, with the failure rate for the sponge being higher.
- The overall failure rate for Reality for the United States sample is not statistically different from failure rates for the diaphragm, sponge, or cervical cap.
- Failure rates for Reality for the total sample and for the United States sample do not statistically differ between parous and nulliparous women or between women who have no education beyond high school and those who do. Failure rates are higher among younger women than among older women who use Reality, although the difference is not statistically significant for users in the United States.

Examination of Table 3 also reveals that while the proportion of women with  $\leq 12$  years of education is very similar among users of Reality in the United States and users of the sponge, cervical cap and diaphragm in the other two trials (roughly 25%), the proportion parous and the proportion aged  $\geq 25$  years in the other two trials (about 20% and 55%, respectively) were far lower than in the Reality trial (60% and 76% in the United States and 72% and 71% overall, respectively). Therefore, one would expect that the comparison of overall failure rates for Reality, the sponge, the diaphragm and the cervical cap is less meaningful than it would be if the composition of users were the same in all three trials. Although the distribution of characteristics of women in each trial cannot be altered after

the trial has been completed, it is possible to compute *standardized* failure rates that reflect the failure rates that would have been observed had the distribution of characteristics been different. For example, Table 3 shows that in the Reality trial, 28.2% (=98/348) of the women were nulliparous and 71.8% were parous. In the sponge trial, the 6-month failure rates among nulliparous and parous women were 9.1% and 19.6%, respectively. The 11.6% overall 6-month failure rate actually observed for the sponge reflects the fact that 74.9% of users were nulliparous and 25.1% were parous. If, instead, the parity distribution in the sponge trial had been the same as the parity distribution in the Reality trial, then the 6-month sponge failure rate would have been  $9.1\% \times 0.282 + 19.6\% \times 0.718 = 16.6\%$ . If the parity distribution in the sponge trial had been the same as the parity distribution among users of Reality in the United States, then the 6-month sponge failure rate would have been  $9.1\% \times 0.403 + 19.6\% \times 0.597 = 15.4\%$ .

In Table 4 and in Figure 2, failure rates standardized by parity, education and age are displayed. These are simply the weighted averages of the probabilities by parity, education or age in Table 3. Two sets of weights are employed: the proportions nulliparous and parous or with  $\leq 12$  years of education and  $> 12$  years of education or aged  $< 25$  years and  $\geq 25$  years (1) among users of Reality in the United States and (2) among users of the sponge, cervical cap or diaphragm.

Because the proportion of women with  $\leq 12$  years of education is similar in all groups except users of Reality in Latin America, standardization by education makes very little difference except among users of Reality in Latin America (not shown). Because failure rates differ appreciably between parous and nulliparous women among users of the diaphragm in the sponge-diaphragm trial, the sponge, and the cervical cap, standardization by parity with weights obtained from users of Reality in the United States changes the failure rates only for these three groups to any great extent; it raises the overall failure rate among users of the sponge and cervical cap and lowers the failure rate among diaphragm users in the sponge-diaphragm trial. If the weights are obtained from users of the sponge, cervical cap and diaphragm, standardization by parity raises the failure rate only slightly among users of Reality in the United States and lowers it among all users of Reality. Because failure rates do not vary much by age among users of the sponge, cervical cap and diaphragm, standardization by age with weights obtained from users of Reality in the United States produces only minor changes in failure rates for these groups. If the weights are obtained from users of the sponge, cervical cap and diaphragm, standardization by age raises the failure rate among users of Reality in the United States and among all users of Reality.

Standardization affects the previous conclusions regarding the comparative efficacy of Reality, the sponge, the cervical cap and the diaphragm in only two of six instances. Standardization by parity appreciably raises the failure rates of the sponge and cervical cap

when the weights are obtained from users of Reality in the United States. Standardization by age appreciably raises the failure rate for Reality when the weights are obtained from users of the sponge, cervical cap and diaphragm. However, parity- or age-standardized failure rates for Reality differ statistically significantly from standardized failure rates for the other methods only for users of the diaphragm, with the failure rate for Reality being higher. Recall that the failure rate for the sponge also differs significantly from the failure rate for the diaphragm in the sponge-diaphragm trial, with the failure rate for the sponge being higher. This standardization exercise reinforces the conclusion that the failure rate for Reality is similar to that for the sponge and cervical cap; the evidence suggests that the diaphragm may have greater efficacy than the other three methods.

Thus far we have considered efficacy at preventing pregnancy among users of barrier methods. However, a contraceptive will have little impact on unintended pregnancy in a population unless those who select a method continue to use it. Therefore, a measure of the population efficacy of a contraceptive is the proportion who continue to use the method. Comparisons of the 6-month discontinuation rates of the Reality female condom, the diaphragm, sponge, and cervical cap are shown in Table 5. Scrutiny of Table 5 reveals that total discontinuation rates are similar for all three clinical trials; however, the percentage lost to follow up (LFU) is far lower for the Reality trial.

### Failure Rates During Perfect Use

Pregnancy rates discussed above reflect efficacy during typical use, where typical use includes a mix of perfect use (correct use according to instructions at every act of intercourse) and imperfect use (either inconsistent or incorrect use). Of equal interest is efficacy during perfect use, since it reflects how well a method prevents pregnancy if it is used correctly at every act of intercourse.

Unfortunately, nearly all investigators who have attempted to calculate "method" and "user" failure rates have done so incorrectly [Trussell and Kost 1987; Trussell and Grummer-Strawn 1990, 1991]. Investigators routinely separate the accidental pregnancies into two groups. By convention, pregnancies that occur during a month in which a method was not always used correctly at every act of intercourse are classified as user failures (even though, logically, a pregnancy might be due to failure of the method, if it was used correctly on some occasions and incorrectly or not at all on others), and all other pregnancies are classified as method failures. There is no problem with this convention for classifying pregnancies. The problem arises because investigators do not separate the exposure (the denominator in the calculation of failure rates) into these two groups.

For example, suppose that there are 2 method failures and 8 user failures during 100 women-months of exposure to the risk of pregnancy. Then the common calculation is that the user failure rate is 8% and the method failure rate is 2%; the sum of the two is the overall failure rate of 10%. The logical error in such calculations is evident when one realizes that method failures — by convention — can occur only during perfect use and that user failures cannot occur during perfect use. If there are 50 months of perfect and 50 months of imperfect use in the total of 100 months of exposure, then the method failure rate would be 4% and the user failure rate would be 16%. To compute perfect-use failure rates, the investigator must be able to identify either periods of perfect use contributed by each woman or those women who always used the method perfectly.

The probabilities of failure during six months of perfect use of Reality by women who met the compliance criteria stipulated in the study protocol were  $5.4\% \pm 2.7\%$  in the United States ( $n = 86$ ) and  $6.0\% \pm 2.4\%$  in the entire sample ( $n = 117$ ); women who reported fewer than four acts of intercourse during the month prior to any follow-up visit, who did not use Reality at every act of intercourse, who ever reported not following the Reality instructions, or who used another method of contraception were excluded from this analysis.

In the sponge-diaphragm and cap-diaphragm trials, information on consistency of use but not on correctness of use is available. Thus, consistent-use failure rates can be readily computed, but these cannot be simply equated with perfect-use failure rates. Failure rates during consistent use provide an upper bound for the failure rates during perfect use because the risk of failure during consistent but incorrect use exceeds the risk of failure during perfect use. In order to get a better idea of the potential difference between failure rates during perfect use and during consistent use, failure rates during consistent use were recalculated after excluding the pregnancies (and corresponding exposure) that were classified as user failure by the clinician. These rates provide a lower bound for the failure rates during perfect use since there are undoubtedly other episodes of consistent but incorrect use during which no pregnancies occurred that should be rightfully excluded. Thus, while precise point estimates of the probability of failure during perfect use cannot be obtained, upper and lower bounds can be provided [Trussell, Strickler and Vaughan 1992]. In the sponge-diaphragm trial, the fractions of women becoming pregnant during six months of perfect use lie between  $8.5\% \pm 1.5\%$  and  $8.8\% \pm 1.5\%$  for the sponge and between  $1.7\% \pm 0.7\%$  and  $2.7\% \pm 0.9\%$  for the diaphragm. In the cap-diaphragm trial, the fractions of women becoming pregnant during six months of perfect use lie between  $4.3\% \pm 1.1\%$  and  $5.8\% \pm 1.3\%$  for the cervical cap and between  $3.1\% \pm 1.0\%$  and  $4.7\% \pm 1.2\%$  for the diaphragm [Trussell and Strickler 1992].

These comparisons reveal that the probability of failure during perfect use of Reality is very similar to that for the cervical cap, slightly lower than that for the sponge and slightly higher

than that for the diaphragm, though none of the differences are statistically significantly different from zero. The fact that the differences in the protocols for the three trials would lead one to expect higher failure rates for Reality if the contraceptive efficacies of the methods were equal only reinforces the conclusion that the efficacy of Reality during perfect use is similar to the efficacies of the sponge, cervical cap and diaphragm during perfect use.

### Six-month *versus* Twelve-month Failure Rates

Although published reports of contraceptive efficacy typically contain 12-month failure rates (and only 12-month rates), there is no justification for this practice other than convention. Indeed, among contraceptive methods that are designed for longer-term protection — such as Norplant and IUDs, it is conventional to report cumulative failure rates through three or five years. Given the extremely high rates of discontinuation among users of female barrier methods, very large samples would be required to compute failure rates at these higher durations of use. Large samples would be required to produce even 12-month failure rates. Given this reality and the fact that there are currently no female options for reducing the risk of acquiring or transmitting STDs (including HIV), it seems appropriate to evaluate new female barriers that serve to reduce the risk both of unintended pregnancy and of STD infection in well-controlled trials of shorter than 12 months' duration. Life-table rates can be compared for any given duration so long as that duration is common across methods. A comparison of the Reality female condom, the sponge, the cervical cap and the diaphragm has shown that the contraceptive efficacies of these methods through six months of use are statistically indistinguishable among users in the United States.

Because 12-month failure rates have assumed, among some observers, the status of sacred cow — albeit a status with no scientific justification whatsoever — it may prove useful to speculate about the likely 12-month failure rate for Reality. As is shown in Table 6, probabilities of failure in the first six months ( ${}_6q_0$ ) typically exceed probabilities of failure in the second six months ( ${}_6q_6$ ) in the sponge-diaphragm and cap-diaphragm trials. Indeed, for both education, parity and age groups among users of the sponge and cervical cap, there are no exceptions to this rule. Exceptions are evident for parous users and older users of the diaphragm in the sponge-diaphragm trial and among all groups of diaphragm users except nulliparous women in the cap-diaphragm trial. Nevertheless, of the 28 comparisons of failure rates in the first six months and in the second six months shown in Table 6, only three are statistically significantly different from zero; in all three of these cases, the failure rate in the second six months is lower than the failure rate in the first six months. If we project the 12-month failure rate for users of Reality in the United States on the basis of the ratio  ${}_6q_6/{}_6q_0$  observed for the sponge, the diaphragm (in the sponge-diaphragm trial), the cervical cap and the diaphragm (in the cap-diaphragm trial), we would obtain estimates of 18.2%,

19.9%, 20.9% and 24.5% respectively. Although it is mechanically possible to produce such 12-month estimates, it is far more meaningful to compare the 6-month failure rate for Reality that is based on clinical data with 6-month failure rates for other methods.

### **Efficacy in STD Prevention**

Couples in the Reality trial were required to be monogamous and not at risk of acquiring a sexually transmitted disease (STD). Therefore, there are no direct clinical data on the efficacy of Reality in reducing the risk of STD transmission. However, data on contraceptive efficacy can be used to provide estimates of the efficacy of Reality as an STD prophylactic.

A 6-month perfect-use probability of contraceptive failure of 5.4% implies that the per cycle probability of conception is reduced by 93.9% [Kestelman and Trussell 1991]. If we assume intercourse occurs twice per week, then on average intercourse will occur once per cycle during the half-week interval when conception can occur. Therefore, it is reasonable to assume that the effectiveness of Reality per cycle at preventing conception is the same as the effectiveness per coital act at preventing STD transmission. Hence, the risk of STD transmission would be reduced by 93.9% at each act of intercourse during which Reality was used correctly.

Suppose that a woman who was not infected with HIV had intercourse twice weekly with a man infected with HIV. If we assume an HIV infectivity of 0.2% per act, then if no prophylaxis were used one in five women would become infected with HIV. In contrast, if Reality were used correctly at every act of intercourse, only one in 79 women would become infected within one year. Under this scenario, the risk of HIV infection per year would be reduced by 93% by perfect use of Reality. The outcome is virtually identical if HIV infectivity is doubled to 0.4% per act or halved to 0.1% per act.

Suppose that failure to prevent HIV transmission is twice as likely as failure to prevent pregnancy. Then perfect use of Reality for one year would still reduce the risk of HIV transmission by 87%. Suppose that use of Reality is not perfect but that instead Reality is used only for every other act of intercourse (or 50% of the time). Although this pattern of use implies that 40% of women would become pregnant within six months (this high a failure rate was not observed among any subgroup of users in the Reality trial), it would nevertheless result in a 44% reduction in the risk of HIV transmission during one year. These analyses demonstrate that use of Reality can be expected to provide highly effective protection against the risk of HIV infection.

## Conclusion

Comparing the contraceptive efficacies of different methods is problematic in the absence of randomized clinical trials [Trussell and Kost 1987]. Because the research design for the clinical trial of the Reality female condom did not include randomization with another method of contraception, no rigorous rock-solid conclusion regarding its comparative efficacy is attainable. Based on less formal comparisons with studies of the contraceptive efficacy of other barrier methods of contraception, we reach the following conclusions:

- The contraceptive efficacy of the Reality female condom is statistically indistinguishable from that of the diaphragm, sponge or cervical cap among women in the United States. Note that even if the contraceptive efficacies of the four methods were identical, one would expect that failure rates for Reality would be higher than those for the other methods since the Reality trial (1) counted chemically confirmed pregnancies even when they were not clinically confirmed, (2) excluded women with low coital frequency, and (3) had a much smaller fraction of the sample LFU.
- The contraceptive efficacy of the Reality female condom is similar to that of the male condom without spermicidal lubricant, though rigorous statistical comparisons are impossible because of the absence of any carefully controlled prospective clinical trials for the male condom.
- Contraceptive continuation among users of the Reality female condom is similar to that among users of the diaphragm, sponge or cervical cap.

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Table 1. Six-month probabilities of contraceptive failure<sup>a</sup> among users of the Reality female condom.

Location	Number Entering <sup>b</sup>	Percent Failing	Standard Error
<i>United States and Latin America</i>	348	15.1	2.3
<i>United States only</i>	238	12.3	2.5
<i>Latin America only</i>	110	22.0	4.8

NOTES:

- a Cumulative gross (associated single decrement) life-table probability  $\times 100$ . All statistics were provided by Family Health International.
- b Ns include 17 women (United States and Latin America), 15 women (United States) and 2 women (Latin America) who never returned for follow up. Therefore, there were 331 women (United States and Latin America), 223 women (United States), and 108 women (Latin America) who contributed exposure to the life-table analyses.

Life  
Table  
12 MoTotal  
ExposureMaximum  
ExposureCharacteristics of the Sample<sup>M</sup>LPU<sup>B</sup> Comments

Comments

Reference	N For Analysis	Life Table 12 Mo	Index	Total Exposure	Maximum Exposure	Characteristics of the Sample <sup>M</sup>	LPU <sup>B</sup>	Comments
Potts and McDewitt (1975)	397	2.1 <sup>d</sup>				77% males ≥ age 40; all married	4.8 <sup>c</sup>	All couples agreed to exclusive use of spermicidally lubricated condom
Peel (1972)	96		3.9	3698 mo	60 mo	All married	2.9 <sup>t</sup>	Hull Family Survey
Glass et al. (1974)	2057	4.2				All white; at recruitment aged 25-39 and married; at enrollment, all women had been using diaphragm, IUD, or pill successfully for at least 5 months	<1.0 <sup>y</sup>	Oxford/FPA study
Vessey et al. (1988)	?		4.4	10000 <sup>c</sup> yr	24 mo	All white; at recruitment aged 25-39 and married; at enrollment, all women had been using the diaphragm, IUD or pill successfully for at least 5 months	?	Oxford/FPA study
John (1973)	85		5.7 <sup>c</sup>	261 yr	>7 yr	?	?	Retrospective survey, Britain
Vessey et al. (1982)	?		6.0	4317 yr	24 mo	All white and aged 25-34; all married at recruitment; at enrollment, all women were using diaphragm, IUD or pill successfully for at least 5 months	0.3 <sup>ty</sup>	Oxford/FPA study
Jones and Forrest (1992a)	1728	7.2				Aged 15-44	21.1 <sup>r</sup>	1988 NSFG; X falling when corrected for estimated underreporting of abortion = 14.8; when also standardized = 15.8 <sup>s</sup>
Bracher and Santow (1992)	262	8.1				12% aged < 20, 78% aged 20-29, 11% aged 30+; 56% parity 0; 87% in union	25.1 <sup>r</sup>	Australian Family Survey; first use of method
Schlirm et al. (1982)	1223	9.6 <sup>s</sup>				Aged 15-44; all married	18.2 <sup>r</sup>	NSFG 1973, 1976
Grady et al. (1983)	1223	9.7 <sup>sc</sup>				Aged 15-44; all married	18.2 <sup>r</sup>	NSFG 1973, 1976
Vaughan et al. (1977)	696	10.1 <sup>s</sup>				Aged 15-44; all married	19.0 <sup>r</sup>	NSFG 1973
Grady et al. (1986)	526	13.8 <sup>s</sup>				Aged 15-44; all married	20.6 <sup>r</sup>	NSFG 1982
Westoff et al. (1961)	-212		13.8	10062 mo	?	All married	5.7 <sup>r</sup>	FGMA survey

ES:

Based on Table 6 in Trussell and Kost (1987) and Table 10:2 in Hatcher *et al.* (1990), and updated to include subsequent studies. Cumulative gross (associated single decrement) life-table probability  $\times 100$ . Calculated by James Trussell from data in the article.

24-month probability of failure  $\times 100$ ; 12-month probability not published.

Kost of these studies incorrectly report the loss to follow-up probabilities as the number of women lost at any one time during the study divided by the total number of women entering the study. Thus, these are the percentages presented in the table. However, the correct measure of LFU would be a gross life table probability. When available, 12-month probabilities are denoted by the letter "g."

Nonresponse rate of the entire study.

Standardized:

Vaughan *et al.* (1977) (1973 NSFG) - Intention (the average of probabilities for preventers and delayers);

Grady *et al.* (1983) (1973 and 1976 NSFG) - Intention (our calculation, the average of probabilities for preventers and delayers);

Schlma *et al.* (1982) (1973 and 1976 NSFG) - Intention, age, and income;

Grady *et al.* (1986) (1982 NSFG) - Intention, age, poverty status, and parity;

Jones and Forrest (1992a) (1988 NSFG) - duration, age, marital status and poverty status.

Total for all methods in the study.

The authors report that LFU for "relevant reasons (withdrawal of cooperation or loss of contact)" was 0.3% per year in the 1982 study and "less than 1%" per year for all reasons in the 1974 study. In the 1982 study, women had on average been followed for 9.5 years; if 0.3% are LFU per year, then 2.8% would be LFU in 9.5 years. LFU including death and emigration is about twice as high as LFU for "relevant reasons."

Unless otherwise noted characteristics refer to females.

Table 3. Comparison of 6-month probabilities of contraceptive failure<sup>a</sup> among users of the Reality female condom, the sponge, the cervical cap, and the diaphragm.

Method/Attribute	Number Entering	Percent Failing	Standard Error
<b>Reality trial<sup>b</sup></b>			
<i>United States and Latin America</i>	348	15.1	2.3
Nulliparous	98	12.8	4.4
Parous	250	16.0	2.7
≤12 years of education	147	20.2	4.0
>12 years of education	201	11.7	2.6
<25 years old	102	25.9	5.4
≥25 years old	246	11.1	2.3
<i>United States only</i>	238	12.3	2.5
Nulliparous	96	12.9	4.4
Parous	142	12.1	3.0
≤12 years of education	58	13.2	5.7
>12 years of education	180	12.1	2.8
<25 years old	56	21.9	6.6
≥25 years old	182	9.4	2.5
<b>Sponge-Diaphragm trial<sup>c</sup></b>			
<i>Sponge</i>	720	11.6	1.4
Nulliparous	539	9.1	1.4
Parous	181	19.6	3.6
≤12 years of education	164	14.1	3.4
>12 years of education	551	11.0	1.5
<25 years old	300	11.9	2.3
≥25 years old	415	11.4	1.8
<i>Diaphragm</i>	717	7.7	1.2
Nulliparous	560	8.7	1.4
Parous	155	4.2	1.9
≤12 years of education	170	12.5	3.2
>12 years of education	542	6.1	1.2
<25 years old	335	11.1	2.1
≥25 years old	378	4.6	1.2

Table 3, Continued.

Method/Attribute	Number Entering	Percent Failing	Standard Error
<b>Cervical Cap-Diaphragm trial<sup>d</sup></b>			
<i>Cervical Cap</i>	687	10.2	1.8
Nulliparous	566	8.8	1.4
Parous	117	18.0	4.5
≤12 years of education	167	16.8	3.8
>12 years of education	510	8.3	1.5
<25 years old	310	9.9	2.1
≥25 years old	377	10.4	1.9
<i>Diaphragm</i>	707	8.3	1.3
Nulliparous	592	8.2	1.4
Parous	114	9.2	3.6
≤12 years of education	182	13.1	3.2
>12 years of education	512	6.5	1.4
<25 years old	315	9.3	2.1
≥25 years old	392	7.2	1.6

## NOTES:

- a Cumulative gross (associated single decrement) life-table probability  $\times 100$ .
- b All statistics were provided by Family Health International. Ns include 17 women (United States and Latin America) and 15 women (United States) who never returned for follow up. Therefore, there were 331 women (United States and Latin America) and 223 women (United States) who contributed exposure to the life-table analyses.
- c Statistics obtained from Trussell and Strickler [1992]. Ns include 61 women (sponge) and 85 women (diaphragm) who never returned for follow up. Therefore, there were 659 women (sponge) and 632 women (diaphragm) who contributed exposure to the life-table analyses. Ns for subgroups may not add to the total N because of missing data on characteristics.
- d Statistics obtained from Trussell and Strickler [1992]. Exposure in the life table starts at the one-week follow-up visit because women were instructed to use an adjunct method of contraception during the first week adjustment period. Ns include 111 women (cap) and 146 women (diaphragm) who never returned for follow up after the one-week visit. Therefore, there were 576 women (cap) and 561 women (diaphragm) who contributed exposure to the life-table analyses. Ns for subgroups may not add to the total N because of missing data on characteristics.

Table 4. Comparison of 6-month probabilities of contraceptive failure<sup>a</sup> among users of the Reality female condom, the sponge, the cervical cap, and the diaphragm, standardized by education, parity and age.

Method/Attribute	Observed	Standardized on Users of Reality in the United States <sup>b</sup>		
		Parity	Education	Age
Reality trial				
United States and Latin America	15.1	14.7	13.8	14.6
United States only	12.3	12.4	12.4	12.3
Sponge-Diaphragm trial				
Sponge	11.6	15.4	11.8	11.5
Diaphragm	7.7	6.0	7.7	6.1
Cervical Cap-Diaphragm trial				
Cervical Cap	10.2	14.3	10.4	10.3
Diaphragm	8.3	8.8	8.1	7.7

Method/Attribute	Observed	Standardized on Users of the Sponge, Cervical Cap and Diaphragm <sup>c</sup>		
		Parity	Education	Age
Reality trial				
United States and Latin America	15.1	13.4	13.8	17.7
United States only	12.3	12.7	12.4	15.0
Sponge-Diaphragm trial				
Sponge	11.6	11.2	11.8	11.6
Diaphragm	7.7	7.8	7.7	7.5
Cervical Cap-Diaphragm trial				
Cervical Cap	10.2	10.6	10.4	10.2
Diaphragm	8.3	8.4	8.1	8.1

NOTES:

- a Cumulative gross (associated single decrement) life-table probability  $\times 100$ .
- b Weighted average of the probabilities by parity or education or age in Table 3, where the weights are the proportions nulliparous and parous or with  $\leq 12$  years of education and  $> 12$  years of education or aged  $< 25$  years and aged  $\geq 25$  years among users of Reality in the United States.
- c Weighted average of the probabilities by parity or education or age in Table 3, where the weights are the proportions nulliparous and parous or with  $\leq 12$  years of education and  $> 12$  years of education or aged  $< 25$  years and aged  $\geq 25$  years among users of the sponge, cervical cap and diaphragm.

Table 5. Comparison of 6-month probabilities of contraceptive discontinuation<sup>a</sup> among users of the Reality female condom, the sponge, the cervical cap, and the diaphragm.

Method	Excluding LFU	LFU <sup>b</sup>	Including LFU
<b>Reality trial<sup>c</sup></b>			
<i>United States and Latin America</i>	39.3	8.1 <sup>d</sup>	44.2 <sup>d</sup>
<i>United States only</i>	32.8	8.6 <sup>d</sup>	38.6 <sup>d</sup>
<b>Sponge-Diaphragm trial</b>			
<i>Sponge</i>	33.9	19.1 <sup>e</sup>	46.4 <sup>e</sup>
<i>Diaphragm</i>	26.6	23.3 <sup>e</sup>	43.7 <sup>e</sup>
<b>Cervical Cap-Diaphragm trial</b>			
<i>Cervical Cap</i>	34.1 <sup>f</sup>	20.0 <sup>g</sup>	46.9 <sup>h</sup>
<i>Diaphragm</i>	36.3 <sup>f</sup>	24.5 <sup>g</sup>	48.5 <sup>h</sup>

NOTES:

- a Cumulative gross (associated single decrement) life-table probability  $\times 100$ .
- b LFU includes both lost to follow up and refused follow up.
- c All statistics were provided by Family Health International.
- d Includes the 4.9% of users in the United States and Latin America and the 6.3% of users in the United States who never returned after the initial visit.
- e Computed from Trussell and Strickler [1992]. Includes the 8.5% of sponge users or the 11.9% of diaphragm users who never returned after the initial visit.
- f Computed from Trussell and Strickler [1992]. Includes the 7.3% of cap users or the 9.1% of diaphragm users who never returned after the initial visit for personal reasons.
- g Computed from Trussell and Strickler [1992]. Includes the 8.9% of cap users or the 11.6% of diaphragm users who never returned after the initial visit and were LFU.
- h Computed from Trussell and Strickler [1992]. Includes the 16.2% of cap users or the 20.7% of diaphragm users who never returned after the initial visit either for personal reasons or because they were LFU.

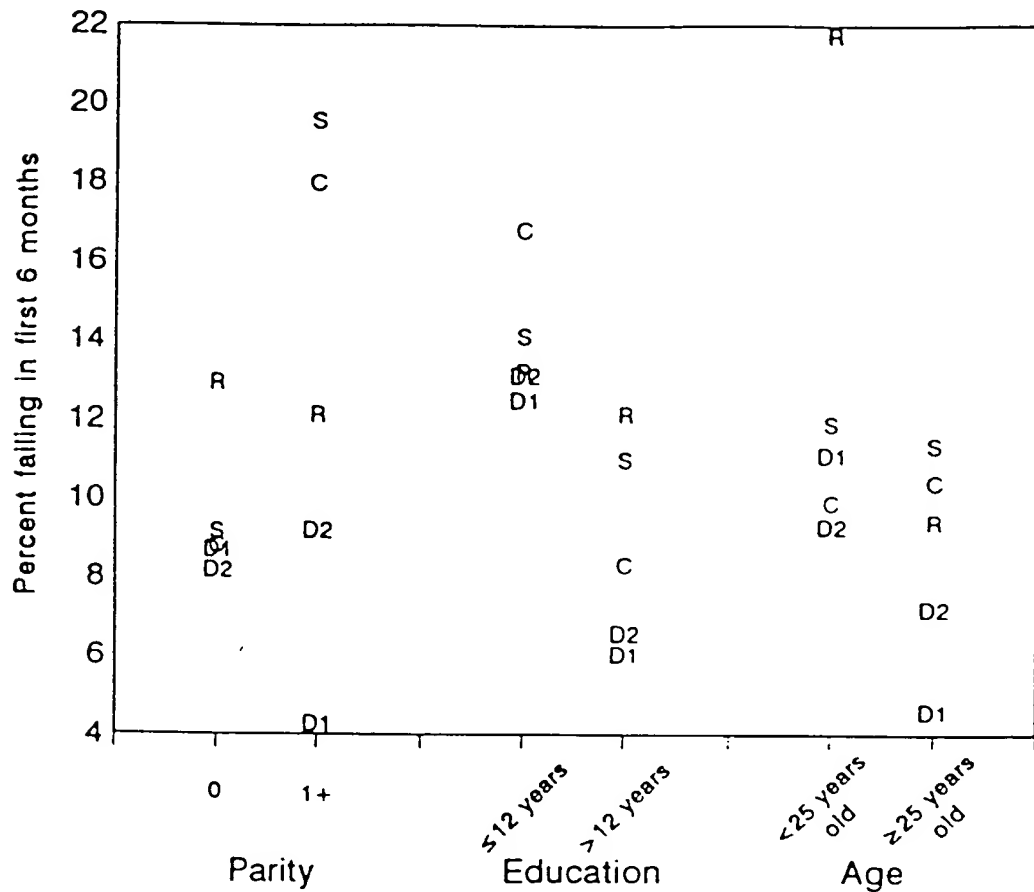
Table 6. Comparison of 6-month and 12-month probabilities of contraceptive failure<sup>a</sup> among users of the sponge, the cervical cap, and the diaphragm.

Method/Attribute	6-month	12-month	Ratio <sup>b</sup> 12 <sup>q</sup> <sub>0</sub> /6 <sup>q</sup> <sub>0</sub>	Ratio <sup>c</sup> 6 <sup>q</sup> <sub>6</sub> /6 <sup>q</sup> <sub>0</sub>
<b>Sponge-Diaphragm trial<sup>d</sup></b>				
<i>Sponge</i>	11.6	17.2	1.5	0.55
Nulliparous	9.1	14.0	1.5	0.59
Parous	19.6	27.4	1.4	0.49
≤12 years of education	14.1	24.5	1.7	0.86
>12 years of education	11.0	15.6	1.4	0.47
<25 years old	11.9	16.9	1.4	0.48
≥25 years old	11.4	17.3	1.5	0.58
<i>Diaphragm</i>	7.7	12.7	1.6	0.70
Nulliparous	8.7	12.8	1.5	0.52
Parous	4.2	12.4	3.0	2.04
≤12 years of education	12.5	21.5	1.7	0.82
>12 years of education	6.1	10.2	1.7	0.72
<25 years old	11.1	16.6	1.5	0.56
≥25 years old	4.6	9.1	2.0	1.03
<b>Cervical Cap-Diaphragm trial<sup>d</sup></b>				
<i>Cervical Cap</i>	10.2	17.5	1.7	0.80
Nulliparous	8.8	15.2	1.7	0.80
Parous	18.0	30.3	1.7	0.83
≤12 years of education	16.8	25.6	1.5	0.63
>12 years of education	8.3	15.2	1.8	0.91
<25 years old	9.9	18.3	1.8	0.94
≥25 years old	10.4	16.6	1.6	0.67
<i>Diaphragm</i>	8.3	16.9	2.0	1.13
Nulliparous	8.2	14.8	1.8	0.88
Parous	9.2	29.0	3.2	2.37
≤12 years of education	13.1	26.6	2.0	1.19
>12 years of education	6.5	13.4	2.1	1.14
<25 years old	9.3	18.6	2.0	1.10
≥25 years old	7.2	15.2	2.1	1.20

**NOTES:**

- a Cumulative gross (associated single decrement) life-table probability  $\times 100$ .
- b Ratio of the 12-month probability of failure to the 6-month probability of failure.
- c Ratio of the probability of failing in months 6-11 to the probability of failing in months 0-5. The probability of failing in months 6-11 is obtained as  ${}_6q_6 = (1 - {}_0q_{12}) / (1 - {}_0q_6)$ .
- d Statistics obtained from Trussell and Strickler [1992].

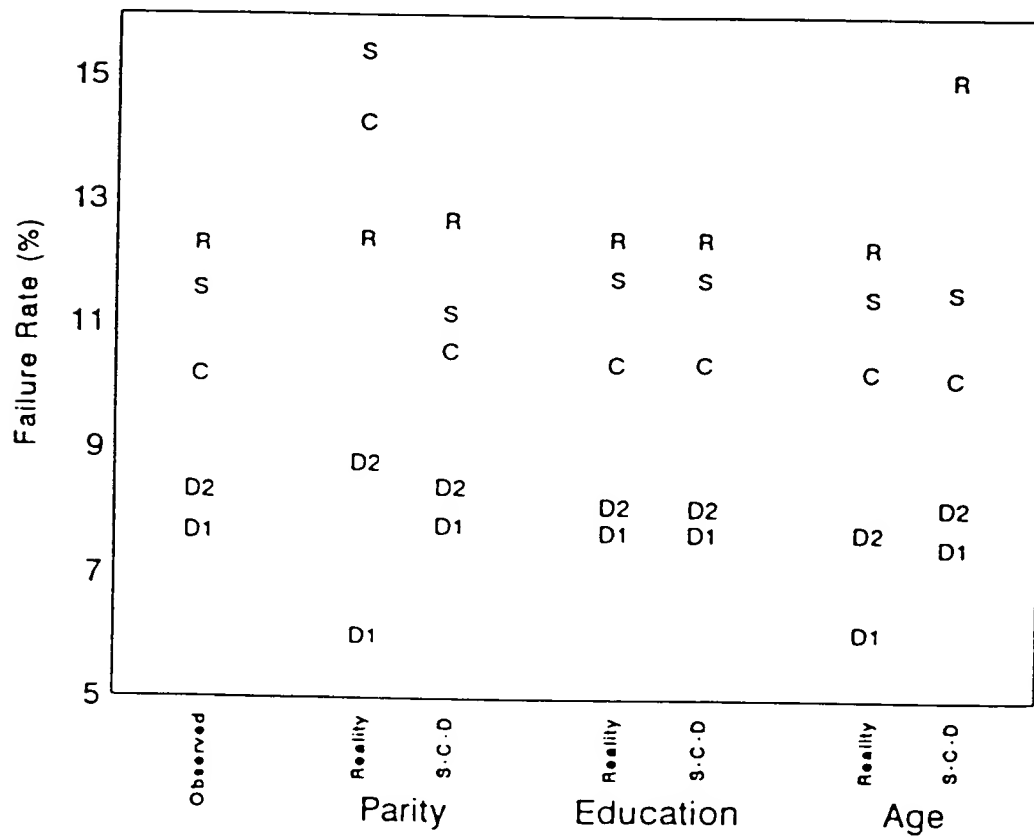
Figure 1: Comparison of 6-month probabilities of contraceptive failure among U.S. users of the Reality female condom, the sponge, the cervical cap, and the diaphragm



#### Key to Symbols

- R Users of Reality in the United States
- S Users of the sponge in the sponge-diaphragm trial
- D1 Users of the diaphragm in the sponge-diaphragm trial
- C Users of the cervical cap in the cap-diaphragm trial
- D2 Users of the diaphragm in the cap-diaphragm trial

Figure 2: Comparison of 6-month probabilities of contraceptive failure among U.S. users of the Reality female condom, the sponge, the cervical cap, and the diaphragm, standardized by education, parity, and age



# 6-month probabilities of contraceptive failure among users of the Reality female condom

Location	N	Percent Failing	Standard Error
<i>Total Sample</i>	348	15.1	2.3
<i>United States</i>	238	12.3	2.5
<i>Latin America</i>	110	22.0	4.8

# 12-month probabilities of failure for the male condom

Reference	Percent failing
Potts and McDevitt 1975	2.1
Glass <i>et al.</i> 1974	4.2
Bracher and Santow 1992	8.1
Schirm <i>et al.</i> 1982	9.6
Grady <i>et al.</i> 1983	9.7
Vaughan <i>et al.</i> 1977	10.1
Grady <i>et al.</i> 1986	13.8
Jones and Forrest 1992	15.8

# Comparison of the Reality trial with the sponge-diaphragm and cap-diaphragm trials

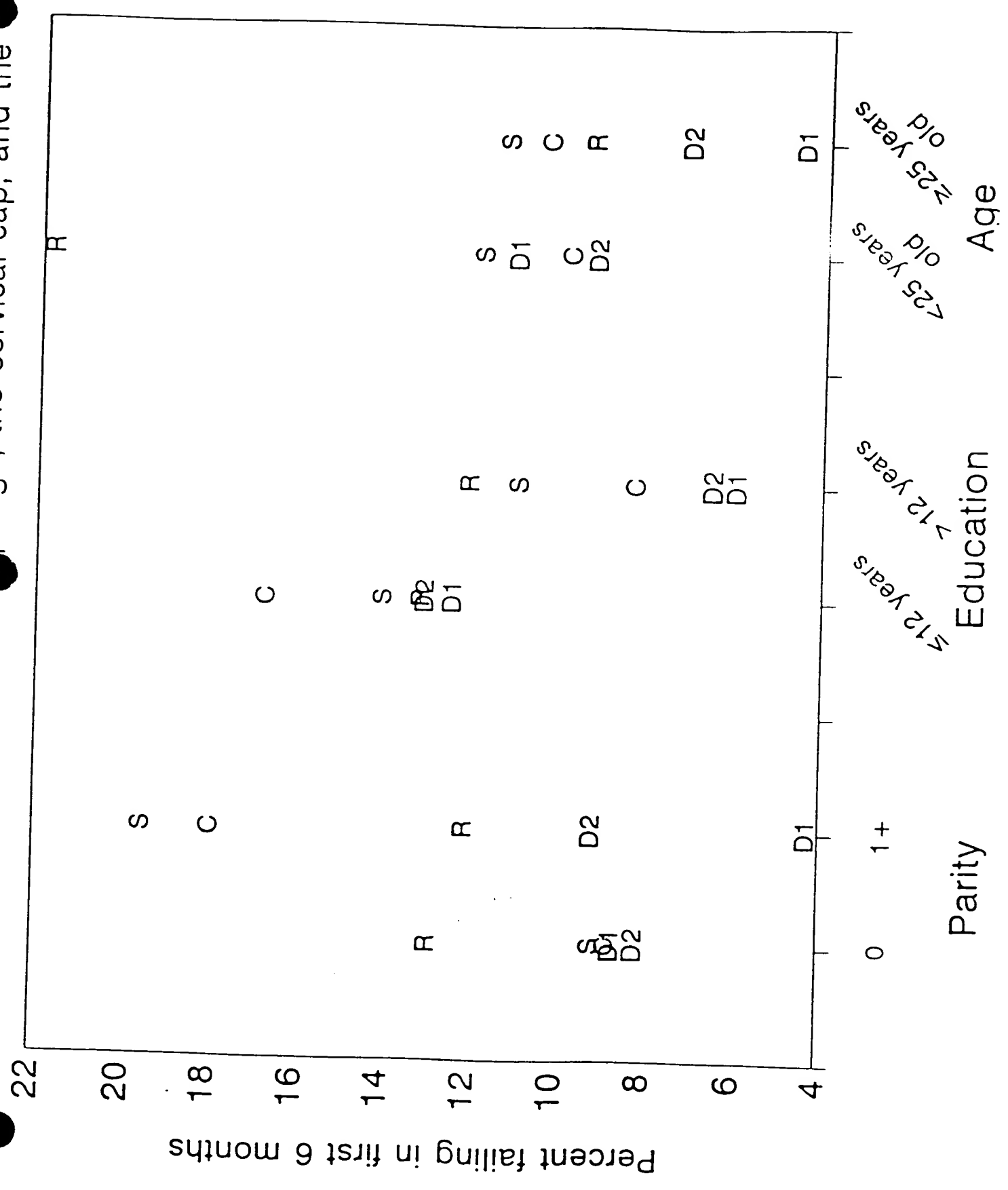
## Reality trial

- performed pregnancy tests at exit and two weeks after exit & counted chemically confirmed pregnancies
- excluded women with low coital frequency
- had much lower loss-to-follow-up rates (9% for Reality US, 21% for S-D, 22% for C-D)

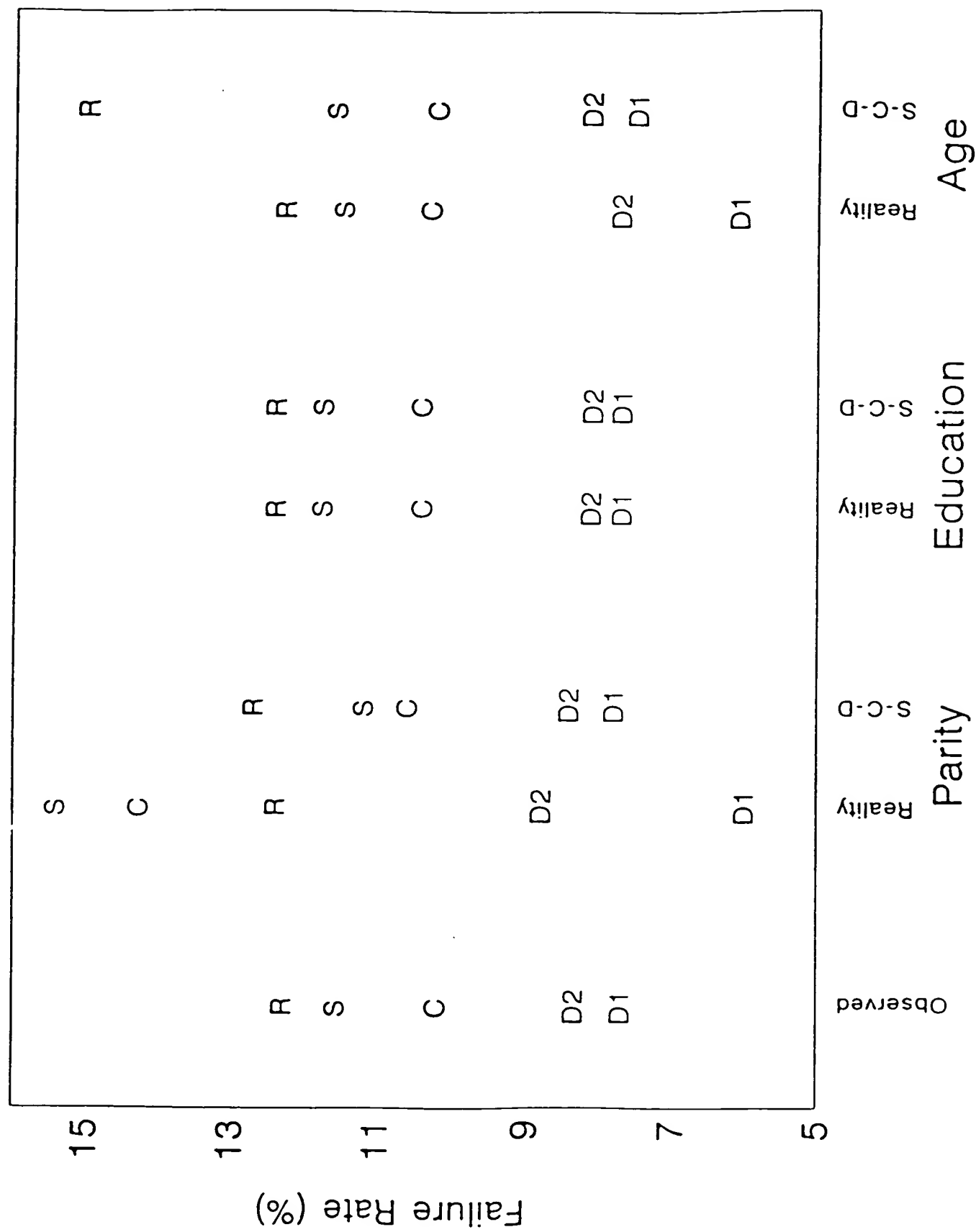
5-month probabilities of contraceptive failure among users of Reality, the diaphragm, the sponge, & the cervical cap.

Method	N	Percent Failing	Standard Error
<i>Reality - US</i>	238	12.3	2.5
<i>Sponge</i>	720	11.6	1.4
<i>Diaphragm</i>	717	7.7	1.2
<i>Cervical Cap</i>	687	10.2	1.8
<i>Diaphragm</i>	707	8.3	1.3

users of the Reality female condom, the sponge, the cervical cap, and the diaphragm.



Comparison of observed probabilities of contraceptive failure among U.S. users of the Reality female condom, the Onge, the cervical cap, and the diaphragm standardized by education, parity and age



6-month probabilities of contraceptive failure during perfect use of Reality, the diaphragm, the sponge, & the cervical cap.

Method	Percent Failing
<i>Reality - US</i>	5.4
<i>Sponge</i>	8.5 - 8.8
<i>Diaphragm</i>	1.7 - 2.7
<i>Cervical Cap</i>	4.3 - 5.8
<i>Diaphragm</i>	3.1 - 4.7

Comparison of 6-month and 12-month probabilities of contraceptive failure among users of the sponge, the cervical cap, and the diaphragm.

Method	6-month	12-month	Ratio $q_6/q_{12}$
<i>Sponge</i>	11.6	17.2	0.55
<i>Diaphragm</i>	7.7	12.7	0.70
<i>Cervical Cap</i>	10.2	17.5	0.80
<i>Diaphragm</i>	8.3	16.9	1.13

● Projection of 12-month probability of contraceptive failure among users of Reality based on results for the sponge, the cervical cap, and the diaphragm.

Based on	% failing within 12 months
<i>Sponge</i>	18.1
● <i>Diaphragm</i>	19.7
<i>Cervical Cap</i>	20.8
<i>Diaphragm</i>	24.3

# HIV PREVENTION

● Model: Kestelman & Trussell *FPP* 1992  
23(5); 226-227, 232

- 6-month perfect-use failure rate of 5.4 implies effectiveness  $e$  per cycle of 93.9
- assume  $e$  per cycle of reducing risk of pregnancy =  $e$  per act of reducing STI
- assume intercourse twice per week and HIV infectivity of 0.2% per act

No prophylaxis:

*1 in 5.3 infected per year*

Perfect use of Reality:

*1 in 79.3 infected per year*

● 93% REDUCTION

*per act* is twice as likely as failure to prevent pregnancy *per cycle*.

- Still 87% reduction in HIV transmission

Suppose use of Reality is not perfect and Reality is used only for every other act of intercourse.

- Although this pattern of use implies a 40% pregnancy rate within 6 months, it would still result in a 44% reduction in HIV transmission during one year.



**Wisconsin  
Pharmacal  
Company**

U A L I T Y   ♦   I N N O V A T I O N

FDA date: 12/1/93

Omend. OCT

*full documentation  
attached*

*Reality*  
Vaginal Pouch  
PMA-P910064 AMEND007 -- 1/21/93

**VOLUME 1**  
FDA QUESTIONS: DECEMBER 21, 1992  
WISCONSIN PHARMACAL RESPONSES

TABLE OF CONTENTS  
PMA-P910064 - Amend 007 - 1/21/93

A. HELIUM LEAK TEST

1. Validation Study

- Attachment A-1 Laser hole pictures
- Attachment A-2 Graph of Sensitivity Results
- Attachment A-3 Raw data - Capability Study
- Attachment A-4 Raw data - Sensitivity Study
- Attachment A-5 Raw data - Reproducibility Study
- Attachment A-6 Raw data - Pressure Study

B. QUALITY ASSURANCE

1. Ring Supplier/Master File

- Attachment B-1 BASF Master File Update Notification

2. Water-Leak Test Validation

- Attachment B-2 Raw data for Water-Leak Sensitivity and Operator Comparison
- Attachment B-3 Raw data for repeated usage of laser holes devices
- Attachment B-4 Raw data for Nominal Hole Size Study

3. Measurement of Water Pressure Generated During Water-Leak Test (Roll)

- Attachment B-5 Protocol, Water-Leak Method and Raw Data

C. PHYSICAL PROPERTIES

1. Seven Day Stability Test (70°C)

- Attachment C-1 7-Day Stability Protocol (with 30-day addendum)
- Attachment C-2 Raw data for 0, 7, and 30 day results  
(*Reality* lots 29100, 49109 and 59100)
- Attachment C-3 Statistical analysis of raw data

C. PHYSICAL PROPERTIES (cont'd)

2. Seam Failure Analysis

- Attachment C-4 • Photomicrograph of *Reality* seam weld, ring weld, and failure analysis (Photos 1-9)
- Pictures of tensile/elongation stress/strain under polarized light (Photos 10-15)

D. TOXICITY

1. Vaginal Irritation Study

- Attachment D-1 Final Report - Vaginal Irritancy Study

2. Sensitization Study, Acute Systemic Toxicity



January 27, 1993

SS

Christine L. Brauer  
Office of Device Evaluation  
c/o PMA Document Mail Center (HFZ-401)  
Center for Devices & Radiological Health  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Subject: PMA P910064; **Reality** Vaginal Pouch

1/27/93  
General 668

Dear Chris:

Enclosed is the response prepared by Dr. Bruce Voeller, to Dave Lytle's questions regarding the bacteriophage permeability study Dr. Voeller conducted at our request on the **Reality** female condom.

I have also enclosed revised sections related to bacteriophage permeability to our response to FDA's March 1992 letter (submitted in July 1992) for Questions #1 and #2, i.e. the summary of safety and effectiveness data and the technical section write-up. For clarity, I have submitted both an annotated revision, i.e. underlined changes, and a "clean" revision for each question.

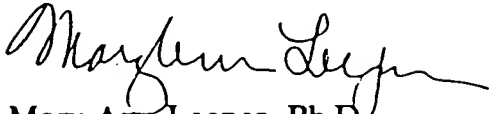
As to Dr. Voeller's response, please note the following:

1. The table referred to as "Dr. R. Bryant's Table 1-05" is the revised Table 14-1 of the original report in the PMA. It is a complete compilation of the data based on a thorough review of the raw data as compiled by an independent consultant to Wisconsin Pharmacal, Dr. Rhys Bryant.
2. Chart A is the revised Table 14-2. This table includes all assays that were repeated.
3. Chart B is a new table and includes all assays that were repeated with non-zero results.

Ms. Christine Brauer  
January 27, 1993  
Page 2

Of course, we are ready to respond to any further questions you may have.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

Enclosures (15 copies)

cc: Dr. L. Yin (letter only)

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax (312) 280-9360



# Wisconsin Pharmacal Company

U A L I T Y     I N N O V A T I O N

February 1, 1993

VIA FAX AND FEDERAL EXPRESS

Christine L. Brauer  
Office of Device Evaluation  
c/o PMA Document Mail Center (HFZ-401)  
Center for Devices & Radiological Health  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

2/2/93

Subject: PMA P910064; **Reality** Vaginal Pouch

Dear Chris:

Enclosed is the authorization letter from Family Health International to Wisconsin Pharmacal giving access to Amendment 2 to their device master file. This amendment contains the information you requested on coital frequency and data pooling.

While this authority letter may not be necessary since cross reference to FHI's master device file was previously given to Wisconsin Pharmacal in September, we are sending this along "just in case."

If you have any additional questions or requests, I am ready to respond to them.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

Enclosure

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541, Fax: (312) 280-9360



**Wisconsin  
Pharmacal  
Company**

QUALITY ♦ INNOVATION

MS. CHRISTINE BRAUER

X NO:

(301) 427-1977

MESSAGE:

Please call (312) 280-8541  
if all pages are not received.

DATE:

2/1/93

PAGES:

3 (including cover)

FROM:

DR. MARY ANN LEEPER

CC:

F 14:15 FAXED D



February 8, 1993

VIA FEDERAL EXPRESS

Christine L. Brauer, Reviewer  
Office of Device Evaluation  
c/o PMA Document Mail Center (HFZ-401)  
Center for Devices & Radiological Health  
Food & Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Re: PMA Amendment 009 to P910064; *Reality* Vaginal Pouch

Dear Ms. Brauer:

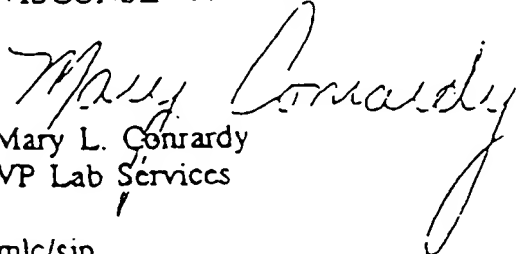
Enclosed are fifteen copies of *Reality* PMA-P910064, Amendment 009.

This amendment responds to your request during the facility inspection January 25 to January 28, 1993. This document includes information on the sensitivity of the helium leak test and water leak test at the top 25 mm of the device, the definition of false positives in the helium leak test, and the water pressure in the roll water-leak test.

Also included are the toxicological studies on the extra lubricant requested by FDA, as discussed in October and the December 21st meeting.

Sincerely,

WISCONSIN PHARMACAL CO., INC.

  
Mary L. Conrardy  
VP Lab Services

mlc/sjp

Enclosure

cc: Dr. Lillian Yin (letter only)



TELECOPY Via (312) 280-9360

Please call (312) 280-8541  
if all pages are not received.

PAGES 1 (with cover)

TO: February 8, 1993  
Ms. Christine L. Brauer

FROM: Dr. Mary Ann Leeper

NO: (301) 427-1977

CC:

MESSAGE:

Dear Chris:

Just to let you know the final tox reports, as well as the answers to the questions you and Bruce raised at the inspection, are being Federal Expressed to you tonight (15 copies).


I'm keeping my fingers crossed -- as far as I can see, this responds to all FDA's questions that we have received to date.

Regards,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

cc: Dr. F. Alan Andersen (301) 427-1977  
Dr. Lillian Yin (301) 427-1977



# Pharmacal Company

A C T I V I T Y   O   I N N O V A T I O N

March 2, 1993

VIA FEDERAL EXPRESS AND FAX: (301 427-1977)

Christine L. Brauer  
Office of Device Evaluation  
c/o PMA Document Mail Center (HFZ-401)  
Center for Devices & Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

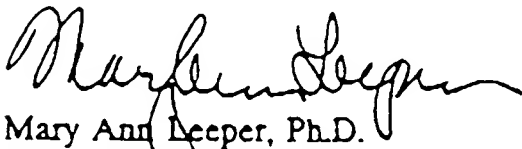
Re: PMA P910064; Reality Vaginal Pouch

Dear Chris:

This responds to your question regarding the site of the manufacture for the secondary lubricant. Wisconsin Pharmacal will manufacture the secondary lubricant:

Wisconsin Pharmacal Company  
2977 Hwy. 60  
Jackson, Wisconsin 53037

Sincerely,



Mary Ann Deeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360



# Pharmaceutical Company

REALITY ♦ INNOVATION

March 2, 1993

VIA FEDERAL EXPRESS AND FAX: (301) 427-1977

F. Alan Andersen, Ph.D.  
Acting Director  
Office for Device Evaluation  
U. S. Food & Drug Administration  
1390 Piccard Drive, HFZ-400, Room 200B  
Rockville, Maryland 20850

Re: PMA P910064; Reality Vaginal Pouch

Dear Dr. Andersen:

I appreciate talking with you yesterday, and particularly having your commitment to advise me immediately of any "red flags" that may arise as FDA staff finish their review of the January 21, 27, and 29 responses to FDA's 12/21 questions and the February 8 response to FDA questions at the plant inspection. As I stated, we're anxious to resolve any pending issues and will attempt to respond to FDA questions immediately.

To clarify the European manufacturing site question, as I stated, there is no pending application on the Chartex facility because Chartex has not completed process validation. When Chartex completes a process validation which is similar to that demanded by FDA of Wisconsin Pharmaceutical, we will file a PMA supplement to permit product manufactured by Chartex to be sold in this country. Prior to submitting such a supplement, we would like to schedule a meeting with FDA officials to discuss what is required. Wisconsin Pharmaceutical recognizes that the review of the PMA supplement will include scheduling an inspection of a foreign site and that the whole process can be time consuming.

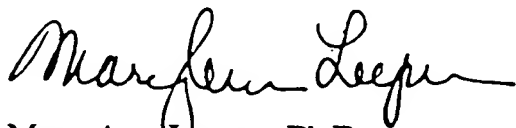
F. Alan Andersen

March 2, 1993

Page 2

In the meantime, we are anxious to finalize the **Reality** labeling and any other questions which FDA staff may have so that **Reality** can be made available to U.S. women - particularly those who are at risk to HIV, and pregnancy, and who for whatever reasons are not currently protecting themselves.

Sincerely,



Mary Ann Leeper, Ph.D.

Senior Vice President of Development

cc: Ms. Amanda Pedersen (Via Federal Express and Fax 301/227-6807)  
Dr. Lillian Yin (Via Federal Express and Fax 301/427-1977)

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax (312) 280-9360

Food and Drug Administration  
Rockville MD 20857

March 22, 1993

MAR 25 1993

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development  
Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

Dear Dr. Leeper:

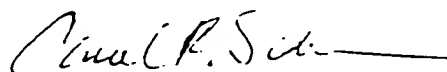
Thank you for your letter to Dr. Kessler of February 11, 1993, concerning the status of the evaluation by the Food and Drug Administration of Wisconsin Pharmacal's Reality™ female condom.

On February 24, 1993, I chaired a meeting between FDA staff and representatives of various health advocacy groups interested in the status of the Reality™ product. This was a followup to a comparable meeting on December 7, 1992. Enclosed are the minutes of the February 24 meeting.

FDA staff noted that in January and February 1993, Wisconsin Pharmacal had made additional data submissions as part of an agreement following the December 10, 1992, advisory committee meeting. We clarified that FDA staff have not yet completed their review of the data, and that work continues on other issues raised at the panel meeting (postmarket studies, marketing and promotion restrictions, and educational programs for consumers).

FDA is committed to reviewing the data submitted by Wisconsin Pharmacal and working closely with you to address outstanding issues.

Sincerely yours,



Carol R. Scheman  
Deputy Commissioner  
for External Affairs

Enclosure

**MEMORANDUM OF MEETING**

**February 24, 1993, 11:30 a.m. - 12:30 p.m.**

**BETWEEN:** FDA: Ms. Scheman, Deputy Commissioner for External Affairs;  
Mr. Grant; Ms. Kuntze; Ms. Pedersen; Ms. Suydam; Dr. Andersen;  
Dr. Merkat; Dr. Bagley; Ms. Cook; Mr. Pollard; Mr. Uldricks;  
Ms. Gangloff

**and Consumer Representatives:**


Cindy Pearson and Toni Young - National Women's Health Network  
Erica Gollub - HIV Center for Clinical and Behavioral Studies  
Lisa Kaeser - Alan Guttmacher Institute  
Irma Maldonado and Elena Alvarado - Mexican Am. Women's Assoc.

**SUBJECT:** Status of the Evaluation of the Reality™ Female Condom

Ms. Scheman stated that FDA initiated this meeting to update interested health advocacy groups about the status of this device--a device important to the women's health community and the first product of a small company. FDA is obliged to help small companies negotiate agency requirements. Ms. Pedersen mentioned the enormous amount of interaction between FDA and Wisconsin Pharmacal over time, including two advisory committee meetings in 1992 to consider the Reality™.

Ms. Suydam reviewed developments since the December 10 panel meeting, including a productive meeting between FDA and the company on December 21, 1992, in which FDA explained specific information the company needed to submit. The company fulfilled a written agreement that came out of the December 21 meeting by making submissions in January and February, 1993, which FDA has not yet fully reviewed. She noted that FDA had conducted a premarket inspection of the Wisconsin facility in January. Ms. Suydam also mentioned other recommendations of the panel (postmarket studies, consumer education, and marketing and labeling restrictions) which FDA is exploring. Ms. Scheman and Dr. Andersen, asked the four groups represented to help in designing consumer education programs. Ms. Scheman pledged continued communication with groups interested in Reality™.

Ms. Pearson mentioned that the National Women's Health Network had no stake in pressing the FDA to approve a product with unanswered safety questions. However, she expressed concern about the time it will take FDA to consider the new data, and said she stated that the Network did want to prod FDA. Ms. Gollub also asked about renewing an IDE that had been denied for the use of Reality™ for research purposes (e.g., to test user acceptability). Dr. Andersen said he would look into the issue and contact her.

  
Linda Gangloff  
Executive Secretariat

## OBSTETRICS and GYNECOLOGY DEVICES PANEL

Chairman

El P. Wager, M.D., M.P.H. 1/31/96  
 Perinatal Associates  
 of Northern Arizona  
 Flagstaff, Arizona

Ring Members

Elizabeth B. Connell, M.D.†  
 Emory University School  
 of Medicine  
 Atlanta, Georgia

Anna F. DeJoseph, C.N.M., Ph.D. 1/31/95  
 University of California  
 San Francisco, California

Henry Dubler, LL.B.†  
 Montefiore Medical Center  
 New York, New York

Thomas K. Goldstick, Ph.D. 1/31/95  
 Northwestern University  
 Evanston, Illinois

Mike Neuman, M.D., Ph.D. 1/31/96  
 Case Western Reserve University  
 Cleveland, Ohio

Robert B. Peterson, M.D.†  
 Centers for Disease Control  
 Atlanta, Georgia

Non-Voting MembersConsumer Representative:

Eryl B. Ruzek, Ph.D. 1/31/93  
 Temple University  
 Philadelphia, Pennsylvania

Executive Secretary

Colin M. Pollard  
 Office of Device Evaluation  
 Center for Devices  
 and Radiological Health (FDA)  
 Rockville, Maryland

Clark K. Colton, Ph.D.†  
 Mass. Inst. of Technology  
 Cambridge, Massachusetts

Thomas D. Downs, Ph.D.†  
 University of Texas  
 Houston, Texas

Gary S. Eglinton, M.D.  
 Georgetown University  
 Washington, D.C.

Joseph Kelaghan, M.D.†  
 National Institutes of Health  
 Bethesda, Maryland

Johanna Perlmutter, M.D. 1/31/95  
 Beth Israel Hospital  
 Boston, Massachusetts

Rochelle N. Shain, Ph.D.†  
 University of Texas  
 San Antonio, Texas

Industry Representative:

Todd J. Polk 1/31/95  
 Cabot Medical Corporation  
 Langhorne, Pennsylvania

† Panel consultants who are specially-designated voting members for today's deliberations on the PMA for the Reality® Intravaginal Pouch



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

APR 2 1993

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development  
Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

APR 7 1993

Re: PMA P910064  
Reality™ Vaginal Pouch


Dear Dr. Leeper:

This is in response to your March 16, 1993, inquiry about Wisconsin Pharmacal's submission to the Food and Drug Administration (FDA) on February 8, 1993.

FDA is reviewing the labeling recommendations discussed at the December 10, 1992 meeting of FDA's Obstetrics-Gynecology Devices Advisory Panel. We will contact you and arrange a meeting to discuss the labeling as soon as possible.

Thank you for your promptness in responding to our questions after our December 21, 1992 meeting.

Sincerely yours,



F. Alan Andersen, Ph.D.  
Acting Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

cc: Ms. Amanda Pedersen

File



QUALITY INNOVATION

4/15/93

April 14, 1993

VIA FEDERAL EXPRESS

'77)

Ms. Christine L. Brauer  
Office of Device Evaluation  
c/o PMA Document Mail Center (HFZ-401)  
Center for Devices & Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Re: PMA P910064; Reality Vaginal Pouch

Dear Chris:

Listed below are the responses to the questions you asked me during our telephone conversation last week:

Question: To update the marketing history of the product, please advise where the devices are currently on the market in Europe, a rough estimate of the number of devices shipped, and how the devices are distributed in the respective markets.

Countries:

- Switzerland (launched in February 1992)
- United Kingdom (launched in September 1992)
- Austria (launched in November 1992)
- The Netherlands (launched in December 1992)
- Portugal (launched in February 1993)
- Norway (launched in March 1993)

Outlets of Distribution:

In all above-mentioned countries, *femidom*® is available as a non-prescription, over-the-counter, broadly distributed device. Typical distribution channels include: pharmacies, drug stores, drug discounters, department stores, and selected food outlets (including major supermarket chains).

Ms. Christine L. Brauer  
April 14, 1993  
Page 2

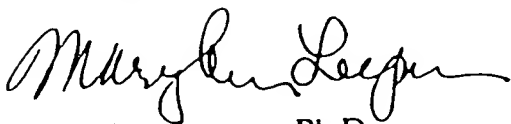
Number of Devices Shipped:

Several million devices have already been shipped to the five European launch markets to-date. This figure is expected to increase as the planned country-by-country roll-out of *femidom*® will cover the rest of Europe and a number of Asian markets by the end of 1993.

Question: In the repeat rip/tear study, was the methodology used in the water-leak testing the same methodology as was process validated and submitted to FDA?

Yes.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax (312) 280-9360



# Office of the Center Director

## Fax Transmittal Sheet

To: Roger Theis

Blaney Ann Leeper

Fax No: 202-737-9329

From: CDRH

Phone No: \_\_\_\_\_ Fax No: \_\_\_\_\_

Number of Pages (including cover sheet): 16

Comments: Revised Labeling - Confidential

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

APR 21 1993

REVISED LABELING FOR THE REALITY™ VAGINAL POUCH  
DRAFT

The following statement will appear prominently on the carton and device package. It will also appear prominently (highlighted or in a box) as the first statement on the instructions for use.

Important Information:

- Latex condoms for men are the best protection against sexually transmitted diseases, including AIDS (HIV infection).
- If the man cannot use a latex condom, Reality will give some protection.
- Before you try Reality, be sure to read the directions in the box and learn how to use it properly.

APR 21 1993

A. Package Insert/Instruction Leaflet

Important Information:

- Latex condoms for men are the best protection against sexually transmitted diseases, including AIDS (HIV infection).
- If the man cannot use a latex condom, Reality will give some protection.
- Before you try Reality, be sure to read the directions in the box and learn how to use it properly.

REALITY™ Vaginal Pouch

Reality is intended to be worn by women during sex. It may help prevent pregnancy and sexually transmitted diseases, including AIDS (HIV infection).

Because Reality is new, it may look different to you or you may feel nervous about trying to insert it -- similar perhaps to how you felt the first time you inserted a tampon, or a diaphragm, or the first time you used a male condom. After you become used to Reality, it should become easier and more comfortable to use.

It's important to practice putting Reality in without having sex. Take your time. Get familiar with Reality's different shape and the way it looks. See how it hangs outside the vagina when in place.

1. Product Overview

a. Description

Reality is a soft, loose-fitting plastic pouch that lines the vagina. It has a soft ring at each end. The ring at the closed end is used to put the device inside the vagina and holds it in place. The other ring stays outside the vagina and partly covers the lip area.

Each Reality can only be used for one sex act. If you try to use it again, it will not protect you. Use a new Reality each time you have sex.

b. Precautions

Here are some important things to remember in order to get the best protection from Reality:

- (1) Use Reality every time you have sex. If Reality is not used every time, your risk of becoming pregnant or getting a sexually transmitted disease will be higher.
- (2) Use a new Reality with each sex act. If you re-use Reality, it will not protect you.
- (3) Do not remove Reality's inner ring. This ring helps keep the device in place during use. If you remove the ring, Reality will not work as well.
- (4) Do not use Reality and a male condom at the same time. If you do, both products will be more likely to break.
- (5) Don't tear Reality. Be careful of sharp objects, like rings or jagged fingernails. If Reality should tear, remove it and use a new one.
- (6) Use more lubricant if needed. If the device comes out of the vagina during use, or if the outer ring gets pushed inside, use a new Reality. Also, add some extra lubricant. You can put the lubricant either inside the device or on the man's penis. The lubricant may also make Reality more comfortable to use and may allow the penis to slip easily in and out of the vagina.

### c. About Reality's Effectiveness

#### How Reality was tested

Limited laboratory tests showed that Reality may block the germs that cause sexually transmitted diseases. Reality was only tested in humans for its ability to prevent pregnancy. That's because researchers did not want to take a chance on exposing people in the tests to AIDS and other sexually transmitted diseases. The idea was that if Reality can prevent sperm from entering the woman and causing pregnancy, it can also prevent spreading the germs that cause sexually transmitted diseases.

Reality was not tested for as long, or on as many people, as other contraceptives. Based on the information we have, about one out of four women who use Reality will become pregnant during a year's time. If you must not become pregnant because of a medical condition, talk to your doctor or family planning clinic before using Reality.

If you use Reality properly each and every time you have sex, your risk of pregnancy should be lower than one out of four.

Remember -- like a man's condom, Reality can only work if you use it! Also remember -- if you're trying to prevent pregnancy, there is no "safe" time when you can have sex without protection.

The table below shows the risk of becoming pregnant when Reality is compared with other contraceptive methods. You can see from this that other devices may be more effective than Reality. Other contraceptive products, such as birth control pills, are even more effective in preventing pregnancy.

PERCENT OF WOMEN WHO BECOME PREGNANT  
DURING 12 MONTHS

---

Methods that protect against both  
pregnancy and sexually transmitted  
diseases

Pregnancy rate

Reality\* 23-26%

Condom<sup>1</sup> 15%

Methods that protect only against  
pregnancy

Pregnancy rate

Cervical Cap 17%

Diaphragm 17%

Sponge 17%

Pregnancy rate

Unprotected sex <sup>2</sup> 85%

- \* Based on a study of about 150 women for 6 months. Yearly failure rates for Reality were estimated by multiplying the 6-month failure rate by 1.8 (23%) and 2.0 (26%). Because this study was limited in size, actual pregnancy rates may be higher or lower.
- <sup>1</sup> 1988 National Survey of Family Growth.
- <sup>2</sup> Trussell, et.al. Studies in Family Planning 21(1), Jan/Feb 1990.

d. When to Use Reality

Reality can be inserted up to 8 hours before sex. However, most women insert Reality between 2 to 20 minutes before sex.

Reality should be removed after sex and before you stand up. It is for one-time use. Use a new Reality with each sex act.

2. Problems using Reality - Some women have reported problems using Reality. In the clinical studies, Reality was pushed inside the vagina 3-18% of the time, and broke less than 1% of the time. Some women have also reported that the penis slipped past the device on entry. Other problems included difficulty inserting the device, irritation and discomfort.

3. Storage Instructions

Store Reality at normal room temperature. Do not use Reality after its expiration date because it may be more likely to break.

**SOME FEATURES OF USING REALITY**

- You can insert Reality yourself. It gives you a way to protect yourself.
- Reality warms up as soon as you insert it. It is both strong and soft.

## INSTRUCTIONS FOR USE

### To Open the Packet

- Pull the two sides of the packet apart from the center of the top.
- Take out Reality and look at it closely.
- Rub the outside of the pouch together to be sure the lubrication is evenly spread inside.
- To add more lubricant, simply give one quick squeeze of the extra lubricant. Try different amounts to see what's best for you and your partner. Try starting with x amount (e.g., teaspoon, drops, etc.)

### To Insert Reality

- Find a comfortable position. Try standing with one foot up on a chair, or sit with knees apart, or lie down.
- Be sure the inner ring is at the bottom, closed-end of the pouch.
- If you wish, add a drop of extra lubricant to the closed-end outside tip of the pouch or to the outside ring before you insert Reality.
- Hold the pouch with the open end hanging down. While holding the outside of the pouch, squeeze the inner ring with your thumb and middle finger.
- Place your index finger between the thumb and middle finger and keep squeezing the inner ring. FIG. C.

- Still squeezing Reality with your three fingers, with your other hand, spread the lips of your vagina and
- Insert the squeezed Reality as shown in FIG. D.

Take your time. If Reality is slippery to insert, let it go and start over.

- Now push the inner ring and the pouch the rest of the way up into the vagina with your index finger, CHECK TO BE SURE THE INNER RING IS UP JUST PAST THE PUBIC BONE. Look at FIG. E. You will feel the pubic bone by curving your index finger when it is a couple of inches inside the vagina. (Please label the pubic bone on the diagram.)

This step may be hard to do on the first or second try because Reality is lubricated.

Take your time and push Reality up to where you can feel the bone.

Make sure Reality is inserted straight (not twisted) into the vagina. It is also important that the OUTSIDE RING LIES AGAINST THE OUTER LIPS AS SHOWN IN FIG. F.

About one inch of the open end will stay outside your body. See FIG. F. While this may look unusual, this part of Reality helps protect you and your partner during sex. Once the penis enters, the vagina will expand and the slack will decrease.

Until you and your partner become comfortable using Reality, use your hand to guide the penis into the pouch. See FIG. G.

After two or three times, you should become familiar with using Reality and should hardly notice the sheath or the outer

ring during sex. For added comfort, you may want to add more lubricant either inside or outside Reality. Some couples like to add extra lubricant directly to the penis.

#### During Intercourse

You may notice that Reality moves around during sex. See FIG. H.

- Movement side-to-side of the outer ring is normal.
- Sometimes Reality may slip up and down in the vagina. If you notice Reality is slipping, add lubricant to the penis or inside the pouch.
- If you begin to feel the outer ring being pushed into the vagina, STOP. See figure x. If the penis starts to enter underneath or beside the sheath, STOP. See figure y. Take out Reality. Put it in a new Reality, and add extra lubricant to the opening of the pouch or on the penis. Make sure the outside part lies over the lip area.

### After Intercourse

To take out Reality, squeeze and twist the outer ring to keep the sperm inside the pouch. Pull out gently. Throw away in a trash can. Do not flush. Do not reuse. FIG. I.

### Remember

To help reduce your risk of pregnancy and spreading or getting a sexually transmitted disease:

- Use a new Reality every time you have sex.
- Follow the directions carefully.
- Be sure you don't tear the sheath with fingernails or other sharp objects.
- Use enough lubricant.

## Questions You May Have About the Proper Use of Reality

### 1. WILL REALITY ALWAYS PROTECT AGAINST PREGNANCY AND STDs?

No method is 100 percent effective. For protection against sexually transmitted diseases, including AIDS, latex condoms for men are the best method. If the man cannot use a latex condom, Reality will give some protection.

### 2. HOW DO I KNOW WHEN REALITY IS UP FAR ENOUGH?

Using your index finger, push the device so that the lower end of the device is against the pubic bone. You will find the pubic bone by curving your index finger when it is a couple of inches inside the vagina.

### 3. WHAT DO I DO IF THE OUTER RING IS PUSHED INSIDE THE VAGINA?

STOP. Remove Reality. Insert a new Reality according to the directions. Put extra lubricant at the opening of the vagina (Do you mean inside or outside the device or both?). Consider lubricating the penis also. This problem can occur if there isn't enough lubricant, or if the inner ring isn't in the proper position.

### 4. WILL REALITY BE NOISY DURING SEX?

If properly lubricated, there should be little noise. If you experience noise during sex, add extra lubricant.

### 5. WHAT IS THE PURPOSE OF THE LUBRICANT?

The lubricant helps the penis move freely in and out, prevents slipping, and discomfort. If the penis does not slip in and out

easily, add more lubricant.

6. WILL I FEEL REALITY ONCE IT IS IN PLACE?

Some people may feel Reality and some may not if it is properly in place and lubricated.

7. WHAT DO I DO IF THE PENIS IS INSERTED OUTSIDE THE POUCH?

STOP. Remove the penis. Insert a new Reality and make sure the outer ring lies flat over the lip area. When you reinsert the penis, guide it with your hands. Do not let the penis directly touch the vagina.

8. WILL REALITY RIP OR TEAR WHILE I AM USING IT?

Studies show that Reality rips or tears less than 1% of the time. If you think Reality has been ripped or torn, remove it right away, throw it away, and insert a new Reality.

9. WILL REALITY BUNCH UP INSIDE THE VAGINA?

Reality should not bunch up inside if it is inserted right and if there is enough lubricant. If you feel the outer ring begin to slip inside, STOP. Remove Reality. Add extra lubricant at the opening to the vagina (inside the device or outside the device?) before putting it back in.

12. WHAT DOES THE OUTER RING FEEL LIKE DURING SEX?

While aware that the outer ring is there, most women say that once they become comfortable with how it looks, they forget about it and don't think about it during sex.

13. WHAT DO I DO IF REALITY DOES NOT STAY IN PLACE DURING SEX?

If Reality moves down the vagina causing discomfort, either push it back up or remove Reality. If you push it back up, add lubricant. If you remove Reality, use a new one and add extra lubricant.

DO YOU HAVE A QUESTION ON  
HOW TO USE REALITY?  
CALL your doctor or family planning clinic  
or  
CALL 1-800-XXX-XXXX

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

APR 26 1993

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development  
Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

Re: P910064  
Reality™ Female Condom  
Filed: October 29, 1991  
Amended: December 17, 19, and 30, 1991; January 9, 15, and 31, February 26, April 13 and 15, June 24, July 16 and 31, August 3, September 28, October 30, November 16, December 1, 4, 7, 16, and 18, 1992; January 22 and 29, February 2 and 9, March 3, and April 15, 1993

Dear Dr. Leeper:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). The Obstetrics-Gynecology Devices Panel, which also reviewed your PMA, recommended to CDRH at the January 31 and December 10, 1992, panel meetings that the PMA be considered approvable. CDRH concurs and is pleased to inform you that the PMA is approvable subject to your submission of an amendment to include your concurrence with the Conditions of Approval and the conditions specified below, as agreed to during our meeting of April 22, 1993:

Preclinical Requirements

1. Initiate real-time aging studies to demonstrate the chemical and physical stability of the device materials (polyurethane and lubricant) to establish a shelf-life. (Devices from at least three production lots should be used to establish the shelf-life.) Until additional data are available, you may only label your device with a 18-month shelf-life.
2. Provide data from *in vitro* permeability studies, such as the  $\phi$ X174 Bacteriophage Studies, to confirm the barrier properties of your device with respect to sexually transmitted diseases. (Devices from at least three production lots should be tested.)

Our March 26, 1992, letter identified the requirements for the shelf-life studies and the barrier transport studies (copy enclosed).

Device Labeling and Promotion

3. Provide revised patient labeling as agreed upon during our April 22, 1993, meeting. (Enclosed is a copy of this revised labeling.) This labeling

identifies the "key elements" as discussed during the meeting, and notes that Reality™'s 6-month and 12-month pregnancy failure rates and how these rates will be presented have not yet been finalized.

4. Confirm that the "key elements" identified in the labeling will appear in all advertisements and promotions as discussed during the meeting.
5. Provide within 45 days professional labeling for Reality™ to include indications for use, contraindications, warnings, precautions, adverse effects, and instructions for use (see enclosure).

#### Future Clinical

6. Agree to participate in future government sponsored studies of the Reality™ Female Condom. The details of the future participation will be negotiated as the plans progress.

As agreed to during our April 22, 1993, meeting, the Reality™ Female Condom is intended for use for vaginal intercourse. If after approval there are reports of device adverse effects or failures for uses other than vaginal intercourse, you will report these findings to CDRH and submit a supplement requesting to amend the warning section of the device labeling.

The PMA must be amended to include your concurrence with, or suggested revision of, the enclosed "Conditions of Approval" and the conditions specified above.

This is to advise you that, following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report shall be consistent with the data reporting provisions of the protocol. Any update report shall be submitted in three copies as an amendment to the PMA and shall include the FDA reference number assigned to the PMA. CDRH will issue an approval order after the requested information has been reviewed and determined to be acceptable. You may not begin commercial distribution of the device until you have received an approval order.

As provided by 21 CFR 814.44(e)(2), you may amend your PMA as requested, or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20857, within 30 days of the date you receive this letter. A petition for administrative review must be submitted in accordance with general administrative procedures

for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

You should be advised that, pursuant to section 515(e)(3) of the Safe Medical Amendments Act of 1990, the Secretary may temporarily suspend approval and initiate withdrawal of this PMA if the Secretary finds that the device is unsafe or ineffective, or on the basis of new information with respect to the device, which when evaluated together with information available at the time of approval, indicates a lack of showing of reasonable assurance that the device is safe or effective under the conditions of the use prescribed, recommended or suggested in the labeling thereof.

The above requested information must be submitted in the form of an amendment, 6 copies. Unless you amend this PMA to request an extension, and the extension is approved, FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). Any request for an extension must be submitted within the 180-day period, justify the need for the extension, and provide a reasonable estimate as to when the requested information will be submitted.

All amendments to the PMA must be submitted in triplicate to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

If you have any questions concerning this approvable letter please contact Mr. Colin M. Pollard at (301) 427-1180 or Ms. Melpomeni Jeffries at (301) 427-1186.

Sincerely yours,



David L. West, Ph.D.  
Deputy Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosures



**Pharmaceutical  
Company**

QUALITY ♦ INNOVATION

if all pages are not received.

DATE:

4/27/93

PAGES:

3 (including cover)

FROM:

M. Leeper

DR. LILLIAN YIN

FDA date: 4/28

NO: (301) 427-1977

CC:

Dave West

MESSAGE:

The press release follows. It will be released in the next hour.

We've tried to recognize the hierarchy and have listed the four conditions.

I'll call you in about 20 minutes.

Regards,

Maylene Leeper

FAXED  
8:43



FOR IMMEDIATE RELEASE  
April 27, 1993

CONTACT: Dr. Mary Ann Leeper  
Senior Vice President,  
Development  
(312) 280-8541  
(Reality Product  
Information)

NASDAQ Symbol: WPCI

John A. Wundrock  
President and C.E.O.  
(414) 677-4121  
(Company Information)

### WISCONSIN PHARMACAL RECEIVES FDA "APPROVABLE LETTER" FOR Reality, THE FIRST FEMALE CONDOM

JACKSON, Wis - Wisconsin Pharmacal Company today received an "Approvable Letter" from the U.S. Food and Drug Administration (FDA) for the company's Reality female condom. This letter signals the FDA's intention to grant the product final marketing approval in the near future. When launched, Reality will be the first of a new class of products approved by the FDA to help prevent the spread of AIDS since the epidemic began more than 10 years ago. It will be the only product under a woman's control that helps to prevent sexually transmitted diseases (STDs), including AIDS, as well as unintended pregnancy.

Women are the fastest growing group contracting AIDS today. By the year 2000, it is estimated that more women than men will be newly infected with HIV through heterosexual intercourse. In addition, approximately 56% of all pregnancies in the U.S. are unintended pregnancies of which approximately 66% occur in young women.

"We have worked hard with FDA to complete the necessary documentation," said Mary Ann Leeper, PhD., the company's Senior Vice President, Development. "Discussions are ongoing to finalize the product labeling. Recently public health agencies have initiated a new campaign to increase awareness that latex male condoms are effective at preventing STDs, including AIDS. Once approved, women will be able to use the **Reality** female condom. This is important when the male condom is not an option."

The "Approvable" status is based on the preclinical and clinical studies completed to date. While **Reality** has not been tested as extensively as other barrier contraceptives, the studies, involving over 1,700 women and 30,000 uses of the device, demonstrate that **Reality** prevents pregnancy and reduces the risk of STDs, including AIDS.

The "Approvable Letter" includes certain post-marketing conditions of approval. Once expected production levels occur at the Wisconsin Pharmacal facility, the company will (1) conduct long term shelf-life studies and, (2) repeat the barrier permeability study. In addition, Wisconsin Pharmacal is required to conduct focus group studies on the final labeling and participate in a large-scale, federally funded clinical study.

Mr. John Wundrock, President and Chief Executive Officer, indicated he is pleased with receipt of an "Approvable Letter" and FDA's expedited review of the **Reality** Pre-Market Approval Application.

**Reality** is currently marketed as *femidom*® by Chartex International or its partners in the United Kingdom, Switzerland, Austria, Portugal, The Netherlands, and Norway.



*Attach  
labeler  
6 sets*

*5/6/83  
Amend 0011*

May 6, 1993

VIA FEDERAL EXPRESS AND FAX (301/427-1977)

Lillian Yin, Ph.D.  
U. S. Food & Drug Administration  
Division of Obstetrics/Gynecology, Ear, Nose, Throat and Dental Devices  
1390 Piccard Drive  
Rockville, Maryland 20850

Dear Dr. Yin:

Re: PMA P910064 - Reality Female Condom  
Amendment 0011

Dear Dr. Yin:

This amendment responds to the approvable letter dated April 26, 1993, with reference to the above-captioned PMA.

Wisconsin Pharmacal Company agrees to the Conditions of Approval and other conditions stated in the letter as modified by conversations on April 27, 1993, and May 5, 1993.

The modifications are stated below:

1. Wisconsin Pharmacal agrees to conduct post-marketing focus groups to review the final labeling to ensure that the labeling is understandable (April 27, 1993). This modification to the approval letter reflects our discussions and agreements during meetings on April 22 and 23, 1993.
2. Pages 5 and 6 of the labeling attached to the April 26, 1993, letter were amended in our conversation of May 5, 1993. These modifications (as telecopied to us on May 5, 1993) are to be incorporated in the final labeling.

Lillian Yin, Ph.D.

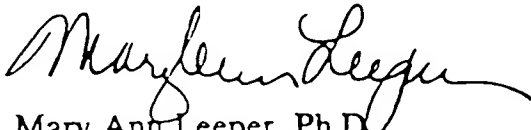
May 6, 1993

Page 2

Safety Update

Wisconsin Pharmacal Company has not conducted and is not aware of any ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

Enclosure

MAL/dlp

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax (312) 280-9360

## Memorandum

Date MAY 7 1993

From Deputy Director, Office of Device Evaluation (HFZ-400)  
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Reality™ Female Condom - ACTION

To The Director, CDRH  
Through: ORA \_\_\_\_\_

ISSUE

Publication of a notice announcing approval of the subject PMA.

FACTS

Tab A contains a FEDERAL REGISTER notice announcing:

1. a premarket approval order for the above referenced medical device (Tab B); and
2. the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION

I recommend that the notice be signed and published.



David L. West, Ph.D.

Attachments

Tab A - Notice

Tab B - Order

Tab C - S & E Summary

DECISION

Approved \_\_\_\_\_ Disapproved \_\_\_\_\_ Date \_\_\_\_\_

Prepared by CDRH, HFZ-470, CLBrauer, CDlytle, and BAHerman, (5/5/93), 427-1180.

cc: HFC-10 (w/original attachments and one copy)  
HFZ-401 DMC (with attachments)  
HFZ-402 PMA (with attachments)  
HFZ-470 ODE (with attachments)  
603:4-22-91

Format for Federal Register Notice (General)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. \_\_\_\_\_]

Wisconsin Pharmacal Company, Inc.; PREMARKET APPROVAL OF Reality™ Female  
Condom

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Wisconsin Pharmacal Company, Inc., Jackson, WI, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Reality™ Female Condom. After reviewing the recommendation of the Obstetrics-Gynecology Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant by letter on MAY 7 1993, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD. 20857.

FOR FURTHER INFORMATION CONTACT:

Colin M. Pollard

Center for Devices and Radiological Health (HFZ-470),

Food and Drug Administration,

1390 Piccard Drive,

Rockville, MD 20850

301-427-1180.

SUPPLEMENTARY INFORMATION: On October 29, 1991, Wisconsin Pharmacal Company, Inc., Jackson, WI, 53037, submitted to CDRH an application for premarket approval of Reality™ Female Condom. The device is a intravaginal barrier device and is indicated for use to help prevent pregnancy and sexually transmitted diseases (STD's), including the human immunodeficiency virus (HIV) infection during vaginal intercourse.

On January 31 and December 10, 1992, the Obstetrics-Gynecology Devices Panel, an FDA advisory panel, reviewed and recommended approval of the application. On           , CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and if available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

## OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under Part 12 (21 CFR Part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act Section 520(h), 90 Stat. 554-555, 571 (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: \_\_\_\_\_.

\_\_\_\_\_  
Bruce Burlington, M.D.  
Director  
Center for Devices and  
Radiological Health

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

---

604:4/22/91

Draft:Brandi:4.23.93:Disk#8 B:\Brauer\FED-REG.604

Final:Brandi:5.5.93

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development  
Wisconsin Pharmacal Company, Inc.  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611

MAY 7 1993

Re: P910064  
Reality™ Female Condom  
Filed: October 29, 1991  
Amended: December 17, 19, and 30, 1991; January 9, 15, and 31,  
February 26, April 13 and 15, June 24, July 16 and 31,  
August 3, September 28, October 30, November 16, December 1, 4,  
7, 16, and 18, 1992; January 22 and 29, February 2 and 9,  
March 3, April 15 and 28, and May 6, 1993

Dear Dr. Leeper:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Reality™ Female Condom. This device is indicated for use to help prevent pregnancy and sexually transmitted diseases, including the human immunodeficiency virus infection (HIV), during vaginal intercourse. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). At the April 22, 1993, meeting between CDRH and Wisconsin Pharmacal, you agreed to the specific conditions listed below with the exception of two specific points on the device labeling. These points were the pregnancy rates at 6 and at 12 months for your product (13% and 26%, respectively) listed on page six of the draft labeling. We note your amendment dated April 26, 1993, including an analysis by James Trussell, your expert on pregnancy failure rates. In view of this amendment, we have revised the table of the draft labeling. These revisions are shown on the following page. The column for the 1-year pregnancy rates must be more prominently high lighted than as shown (e.g., use of borders, shadowing, etc.).

In addition, we have added the following text to the device labeling:

"The pregnancy rate in the 6-month study was 13%. The estimated 1 year pregnancy rate for Reality ranges from 21% to 26%. This means that about one in four women who use Reality may become pregnant during a year."

As part of the heading to the above table just before the sentence "Your risk of pregnancy may be higher or lower...", we have added the phrase "depending on if you use the method correctly every time you have sex....".

We are enclosing these editorial changes and corrections to you as the final draft labeling (copy enclosed).

OVERALL PREGNANCY RATES FOR BARRIER CONTRACEPTIVES

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Condoms Which Protect Against Pregnancy and Sexually Transmitted Diseases

	Pregnancy Rates**	
	<u>6-Months</u>	<u>1 Year</u>
Reality™ Female Condom*	13%	26%
Male Latex Condom <sup>1</sup>	8%	15%

Pregnancy Rates for Other Methods

	Pregnancy Rates**	
	<u>6-Months</u>	<u>1 Year</u>
Cervical Cap	10%	18%
Diaphragm	8%	15%
Sponge	12%	17%

	Pregnancy Rates	
	<u>1 Year</u>	
Unprotected Sex <sup>2</sup>	85%	

\* Yearly failure rates for Reality™ Female Condom were estimated by doubling the 6-month pregnancy rate.

\*\* Pregnancy rates for Reality™ Female Condom, Cervical Cap, and Sponge are from clinical trials. Actual use failure rates may be higher or lower.

<sup>1</sup> 1988 National Survey of Family Growth

<sup>2</sup> Trussell, et.al., Studies in Family Planning 21 (1), Jan/Feb 1990.

The agreed upon conditions of approval were conveyed to you in CDRH's approvable letter dated April 26, 1993. Your May 6, 1993, amendment provided written concurrence with the conditions of approval, and you may begin commercial distribution of the device upon receipt of this letter. Please note that you are required to incorporate these editorial changes and corrections exactly as directed in the device labeling, and to submit to FDA a copy of final patient labeling prior to marketing.

#### Specific Conditions

##### 1. Preclinical Requirements

- a. Initiate real-time aging studies to demonstrate the chemical and physical stability of the device materials (polyurethane and lubricant) to establish a shelf-life. (Devices from at least three production lots should be used to establish the shelf-life.) Until additional data are available, you may only label your device with a 18-month shelf-life.
- b. Provide data from *in vitro* permeability studies, such as the  $\phi$ X174 Bacteriophage Studies, to confirm the barrier properties of your device with respect to sexually transmitted diseases. (Devices from at least three production lots should be tested.)

##### 2. Device Labeling and Promotion

- a. Revise the patient labeling according to the enclosure, and conduct focus group studies to refine the device labeling.
- b. Include the "key elements" identified in the labeling in all advertisements and promotions as discussed during the meeting.
- c. Provide within 45 days of the date of this letter professional labeling for the Reality™ Female Condom. This professional labeling should include indications for use, contraindications, warnings, precautions, adverse effects, and instructions for use (see enclosure).

##### 3. Future Clinical Requirements

Participate in future government sponsored studies of the Reality™ Female Condom. The details of the future participation will be negotiated as the plans progress.

DRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

You should be advised that, pursuant to section 515(e)(3) of the Safe Medical Amendments Act of 1990, the Secretary may temporarily suspend approval and initiate withdrawal of this PMA if the Secretary finds that the device is unsafe or ineffective, or on the basis of new information with respect to the device, which when evaluated together with information available at the time of approval, indicates a lack of showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Colin Pollard at (301) 427-1180 or Melpomeni Jeffries at (301) 427-1186.

Sincerely yours,



David L. West, Ph.D.  
Deputy Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosures

## SUMMARY OF SAFETY AND EFFECTIVENESS

### I. General Information

Generic Name: Female Condom

Trade Name: Reality™ Female Condom

Applicant's Name: Wisconsin Pharmacal Company, Inc.  
2977 Highway 60  
Jackson, Wisconsin 53037

Premarket Approval Application (PMA) Number: P910064

Dates of Panel Recommendations: January 31, 1992  
December 10, 1992

Date of Notice of Approval to Applicant: MAY 7 1993

### II. Indications for Use

The Reality™ Female Condom (hereafter referred to as Reality™) is an intravaginal barrier device, especially for women whose sex partners do not use latex condoms. It is indicated for use to help prevent pregnancy and sexually transmitted diseases (STDs), including the human immunodeficiency virus (HIV) infection, during vaginal intercourse.

### III. Device Description

Reality™ is a loose-fitting polyether polyurethane sheath with two flexible polyether polyurethane rings. One ring lies inside at the closed end of the sheath, and serves as an insertion mechanism and as an anchor during use. The other ring forms the external edge of the sheath and remains outside the vagina after insertion. Once inserted, Reality™ lines the inner contours of the vagina. Reality™ is prelubricated with silicone. An additional water-based lubricant is individually packaged and supplied with each device. Reality™ is for single use only.

### IV. Contraindications, Warnings and Precautions

Use of Reality™ is contraindicated in the presence of any of the following conditions: (1) sensitization to the device materials or lubricant and (2) any active vaginal, vulvar or cervical infection.

The device should not be used by women who are unable to insert or remove device or follow the instructions for use. See the attached labeling for additional warnings and precautions (Attachment 1).

### V. Potential Adverse Effects of the Device on Health

Studies have shown that health risks associated with the use of the Reality™ include discomfort, vaginal irritation, penile irritation, sensitization to

device materials, urinary tract infection, vaginal and cervical infections, sexually transmitted diseases and unintended pregnancy.

## VI. Alternative Practices and Procedures

The latex male condom is the only commercially available product for reducing the risk of pregnancy and STDs, including HIV infection. There are, however, other available methods of contraception. Contraceptive barrier methods include the cervical cap, the diaphragm, the sponge and the condom. Nonbarrier methods of contraception include hormonal methods and intrauterine devices.

## VII. Marketing History

Reality™ is manufactured and distributed in Europe by Chartex International under the trademark Femidom. Femidom has the same product specifications as Reality™. Femidom became commercially available as an over-the-counter device between February 1992 and March 1993 in Switzerland, United Kingdom, Austria, The Netherlands, Portugal and Norway.

## VIII. Summary of Studies

### A. Nonclinical Laboratory Studies

#### 1. Physical and Chemical Properties

The applicant conducted tests to characterize the physical properties of the device. The test methodology for tensile strength and ultimate elongation was the American Society for Testing and Materials (ASTM) D-412. The instrument used to measure these parameters was an Instron Tester. The test methodology for burst pressure and volume was adopted from International Standards Organization (ISO) 4074/6. The test apparatus was a modification of a burst tester used for latex condoms.

The applicant established minimum tensile and burst strengths for the device. The device's minimal cross-grain and with-grain tensile strength at break was established at greater than 35 MPa. The minimal seam tensile strength at break was established at greater than 10.3 MPa. The minimal burst strength was established at 0.7 psi. These physical properties are considered adequate for the intended use of the device.

The device materials, polyether polyurethane, may contain the residual monomer methylene dianiline (MDA), a known animal carcinogen.<sup>1</sup> Samples of silicone-lubricated and non-lubricated Reality™ devices were extracted in 60 ml of distilled water at 37°C for 24 hours. The extracts were analyzed by reverse-phase liquid chromatography. MDA was not detected in any sample extract. The detection limits of the test were 5 parts per billion.

## 2. Biocompatibility:

A series of *in vitro* and *in vivo* biocompatibility tests were conducted on Reality™ and its additional lubricant to evaluate any potential acute and chronic toxicity, and to demonstrate the safety of the device materials for their intended use.

### a. In-Vitro Toxicity

1. Cytotoxicity: A non-lubricated Reality™ device was tested according to U.S. Pharmacopeia procedures for cytotoxicity in mouse L-929 cells.<sup>2</sup> There were no differences in the cytopathic index and cytotoxic index between the device extract and the negative control.
2. Mutagenicity: Non-lubricated Reality™ devices were extracted in saline (0.9%) and ethanol (100%) at 50°C for approximately 76 hours. Extracts were tested in the Ames *Salmonella typhimurium* Test. Neither extract increased the number of his- to his+ *S. typhimurium* revertants in the assay.

### b. Acute Toxicity

1. Primary Dermal Irritation: Non-lubricated Reality™ devices were applied to one intact and one abraded site on the back of six New Zealand rabbits for 24 hours. Testing sites were evaluated for erythema and edema using the Draize criteria. There were no differences in erythema and edema between abraded and intact tissue surfaces at 24 and 72 hours.
2. Dermal Sensitization: The silicone lubricated Reality™ device plus additional water-based lubricant, the additional water-based lubricant alone, and saline (0.9%) and cottonseed oil (100%) extracts of the Reality™ devices were tested using a modified Buehler procedure with 10 albino guinea pigs per group.<sup>3</sup> Testing sites were evaluated for erythema and edema using the Draize criteria approximately 24 and 48 hours after the challenge application. No signs of erythema or edema were observed at the challenge sites.
3. Acute Vaginal Mucosal Irritation: Silicone lubricated Reality™ devices (60cm<sup>2</sup>) were minced, and combined with 10ml of additional water-based lubricant and 10ml of K-Y Jelly. 0.5ml of each test sample was administered into the vaginal vault of 10 white New Zealand rabbits for 5 days. Another group of 10 rabbits was administered either 0.5ml of the additional water-based lubricant or K-Y Jelly for 5 days. The K-Y Jelly was used as a control. Histopathological examinations on all animals were performed and scored by scalar notation. There were no significant differences in the scores between the control and treatment groups. Both were considered mild irritants.

4. Acute Systemic Toxicity: Device extracts were tested according to U.S. Pharmacopeia procedures using five mice per device extract. Silicone lubricated Reality™ devices with and without the additional water-based lubricant were extracted in saline (0.9%), ethanol in saline (5%), cottonseed oil and polyethylene glycol. There were no systemic toxic effects in mice from the administration of any of the extracts.

c. Chronic Toxicity

1. Chronic Vaginal Irritation: Ten white New Zealand rabbits (group 1) received between 20 to 24 treatments of glass beads coated with the silicone lubricated Reality™ device. Ten animals (group 2) received between 20-26 treatments of glass beads which were not coated with the silicone lubricated Reality™ device. Another control group (group 3) received no treatment. The beads, which were secured to a 26cm silk suture, were introduced into the vagina and remained in place for 4 hours.

Histopathologic examinations were conducted on three sections of each vagina and scored by scalar notation. The mean total histological score for the Reality™ coated glass beads was slightly higher than the mean score for the glass beads alone, indicating that the Reality™ coated glass bead caused slight vaginal mucosal irritation.

Silicone lubricated Reality™ devices were extracted with saline (0.9%) and cottonseed oil (100%) according to U.S. Pharmacopeia procedures. Extracts were tested as described above except that a 0.5 ml sample was administered into the vaginal vault. There were no significant differences in mean total histopathological scores between the device extracts and extracts alone.

3. Barrier Transport Studies

a. Methodology

Virus penetration tests were performed in a two chamber, dynamic pressure apparatus. The device was prevented from expanding under pressure by an open-mesh restrainer. The dynamic test included pulsed pressure, with a periodic (30 cpm) trans-membrane peak pressure of 8 psi (over 400mm Hg) and with 43% of the cycle at greater than 2 psig. The surrogate challenge virus was the bacteriophage  $\phi$ X174, which is 27nm in diameter. (Hepatitis B, which is the smallest known STD, is 42nm in diameter.) Nine hundred ml of buffer containing the challenge virus on the upstream (challenge) side contacted the inside of the device, while 212ml of buffer on the downstream side was assayed to detect and quantify any virus which penetrated the device.

Data from quantitative biological assays demonstrated that the test method, including the buffer, the components of the test apparatus, and the entire downstream side of the test setup, did not inactivate the challenge virus during the course of testing a sample device.

Reality™ devices that had laser-induced holes, which were partially characterized by scanning electron microscopy, were used as positive controls. The exit hole size was found to be smaller than the entrance hole size, and varied from sample to sample. Thus, the actual hole size was smaller than the nominal, "entrance", hole size. Virus penetration was determined for devices containing laser-induced holes with nominal sizes of 10, 20, 25 and 100µm. Different nominal 10µm holes allowed an average penetration of 2300nl (range: 520-4100nl) of the challenge virus suspension at 30 minutes.

b. Test Results with Intact Reality™ Devices

Fifteen Reality™ devices were tested with at least 4 samples from 3 different manufacturing lots. The results demonstrated that:

- 8 samples had no detectable virus penetration;
- 6 samples had apparent low-level virus penetration; and
- 1 sample had substantial virus penetration.

Of these 15 samples, there were two samples with evidence of virus contamination during assay and confirmed by reassay. This contamination did not interfere with conclusions regarding virus penetration of the devices.

Of the 6 devices with apparent low-level viral penetration, two cases were confirmed by reassay. Because of statistically low numbers of viral penetration, the other four could not be confirmed. The virus titers in the downstream buffer were indicative of 2-20nl penetration by the challenge virus suspension. One device allowed a higher level of virus penetration which increased with time during the test. The level of virus titer indicated virus penetration from a  $\geq 10\mu\text{m}$  hole.

Tests for virus penetration were also performed with three latex male condoms (with appropriate test system modification for the smaller diameter male latex condoms). These data indicated that no virus penetration was found in those samples.

c. Conclusions

The barrier properties of Reality™, with respect to sexually transmitted diseases, were analyzed in an artificial, laboratory test with a very small surrogate virus ( $\phi\text{X174}$ ). Eight devices allowed no detectable virus penetration; six allowed low level penetration, which given the test conditions, should represent

insignificant virus penetration in actual use. Overall, 14 of 15 devices were significant barriers to virus penetration.

#### 4. Quality Assurance Control Procedures

As an in-line production quality assurance (QA) test, every Reality™ device is tested to detect any pinholes. Helium is introduced into the device's interior and testing for helium is done on the outside environment. Detection is done using a commercially available detector (Mark model 9822) and a custom made holder for Reality™. Validation studies, using 120 devices with laser-induced holes of known sizes at various locations, demonstrated that this test is capable of detecting virtually all pinholes of 20µm or greater, (and most 10µm diameter pinholes) as close as 5mm from the outer ring of the device. This QA procedure is adequate to detect any degradation in manufacturing processes, and to assure the integrity of the device materials with respect to possible pinholes. This QA procedure compares favorably with QA procedures used for latex male condoms.

At end stage manufacture, Reality™ devices are checked with a defined sampling plan for leaks with a test similar to a standard ASTM test for latex male condoms. The devices are filled with water and visually checked for leaks in both vertical and horizontal orientations. Validation studies were conducted with over 600 devices with laser-induced holes at various locations. These studies demonstrated that the test is capable of detecting approximately 90% of 20µm diameter pinholes and over 50% of 10µm diameter pinholes, at locations greater than 30mm from the outer ring of the device. This QA procedure is adequate to assure the integrity of the device materials with respect to pinholes, and is comparable to the water leakage test used for latex male condoms.

#### B. Summary of Clinical Investigations

In response to the urgent public health need for a female barrier devices with the potential to prevent a life threatening disease, HIV infection, the Food and Drug Administration (FDA) developed an expedited study protocol. This expedited study protocol was made available to the public on April 4, 1990, in the form of a guideline entitled "Premarket Testing Requirements for Female Barrier Contraceptive Devices Also Intended to Prevent Sexually Transmitted Diseases". Because of the difficulties in studying STD prevention in clinical studies, the guideline designated pregnancy as a surrogate study endpoint if preclinical laboratory studies demonstrated that the device was an effective barrier to STD-sized particles. To further expedite the approval of such devices, a comparable historical control could be used. The Reality™ device was the first device reviewed by FDA since the development of these guidelines.

The clinical investigations summarized below establish the safety and effectiveness of Reality™. (Some early clinical investigations on prototype devices and data from countries outside the United States and Latin America are not reported below.)

1. Phase I - Dislodgement Study

- a. Study Methods - Study subjects were monogamous sexually active couples not at risk for pregnancy due to oral contraceptive use or sterilization. Each couple used 3 Reality™ devices and 3 latex male condoms in a pre-determined sequence. Study subjects completed a questionnaire on device dislodgement, breakage and acceptability after each use.
- b. Study Population - Fifty couples were enrolled in the study. A total of 49 couples completed the study for a total of 147 uses of Reality™ and 147 uses of the latex condom.
- c. Study Results - Study subjects reported all results by questionnaire. One Reality™ device and one latex condom broke during use (0.7%). Reality™ invaginated (i.e., the outer ring of the device was pushed inside the vagina) 26 out of 147 uses (17.7%), and the latex male condom slipped down the shaft of the penis 12 out of 147 uses (8.2%). There were 80 out of 147 uses where inserting Reality™ was difficult or impossible. Significant discomfort was reported for 19/147 (12.9%) and 1/146(0.7%) uses of Reality™ and latex condoms, respectively.

The breakage, acceptability and dislodgement rates for Reality™ are considered adequate for a female barrier contraceptive device.

2. Phase I - Breakage Study

- a. Study Methods - Study subjects were monogamous sexually-active couples not at risk for pregnancy due to oral contraceptive use or sterilization. Each couple used 5 Reality™ devices and 5 latex male condoms in a pre-determined sequence. Within 12 hours after use, each device was returned via a mail pack and tested via the water leakage test. Study subjects also completed a questionnaire on device dislodgement, breakage and acceptability after use.
- b. Study Population - A total of 53 couples were enrolled in the study, and 44 couples completed the study. One couple discontinued due to partner dislike; 1 due to irritation to both devices; and 7 for personal reasons not related to either test product.
- c. Study Results - There were a total of 471 returned devices, including 237 Reality™ devices and 234 latex condoms. Of the returned devices, 6/237 (2.5%) Reality™ devices and 11/234 latex condoms were not testable (e.g., ripped or torn). Of the testable devices, 2/231 (0.9%) Reality™ devices failed the water leakage test and 5/223 (2.2%) latex condoms failed the water leakage test.

Study subjects reported 61/237 (25.7%) and 33/234 (14.1%) instances, respectively, where inserting Reality™ and the latex condom was difficult or impossible. Study subjects reported significant

discomfort for 11/234 (4.7%) and 13/233 (5.2%) uses of Reality™ and latex condoms, respectively.

The breakage rates and acceptability of Reality™ are considered adequate for a female barrier contraceptive device.

3. Phase 1 - Post Coital Sperm Test Study

- a. Study Methods - This study was conducted at the University of Chicago OB-GYN Outpatient Clinic. Study subjects were not at risk for pregnancy due to oral contraceptive use or sterilization. Study subjects underwent examinations for the presence of sperm in the vaginal vault upon entering the study and within 8 hours after use of Reality™. Study subjects were to use 5 lubricated Reality™ devices and were supplied an additional lubricant with spermicide.
- b. Study Population - Twenty-two study subjects were enrolled in the study, and five were lost to follow-up. Two study subjects used the device for one coital act, and discontinued the study. A total of 15 study subjects completed the study. In one coital episode, the partner failed to achieved ejaculation, leaving a total of 76 evaluable coital episodes.
- c. Study Results - Out of the 76 evaluable coital episodes, sperm was found in the vagina once (1.3%). However, this study subject reported improper use of Reality™, which may have caused this finding. These data are considered adequate for a female barrier contraceptive device.

4. Phase I - Vaginal Trauma Study

- a. Study Methods - This study was conducted at the Medical College of Virginia. Study subjects were not at risk for pregnancy due to oral contraceptive use or sterilization. Study subjects were randomly assigned to use Reality™ or the diaphragm. At the initial and follow-up visits, the vagina, cervix, and vulva of each participant were examined coloposcopically and aerobic, anaerobic, and fungal cultures of the vagina were taken. After the initial visit, study subjects were examined 3 hours post device wear (visit 2), post intercourse and overnight wear (visit 3), and post 7 day-use with a minimum of 5 coital episodes using the device (visit 4).
- b. Study Population - Thirty study subjects were enrolled in this study and randomly assigned to use Reality™ or a diaphragm. Fifteen subjects were randomized to each arm.
- c. Study Results - There was no evidence of significant trauma associated with the use of either contraceptive device. However due to the sample size, low frequency vaginal trauma due to device usage would not be expected to be detected. The resident vaginal flora did not significantly change during the three follow-up visits in study subjects using Reality™. Among diaphragm users, lactobacilli

were less frequently isolated at the third and fourth follow-up visits compared to the initial visit. Also, aerobic Gram negative rods were more frequently isolated at the fourth visit of diaphragm users.

5. Phase II - Trichomonas Reinfection

- a. Study Methods - This study was conducted at six trial sites: University of Chicago, Chicago, Illinois; Medical College of Virginia, Richmond, Virginia; University of Southern California, Los Angeles, California; Georgetown University, Washington D.C.; Yale University, New Haven, Connecticut; and Hahnemann University, Philadelphia, Pennsylvania. Study subjects were sexually active women at least 18 years of age with documented vaginal trichomoniasis. Study subjects were excluded if they relied upon another barrier contraceptive, were pregnant or had a clinical diagnosis of pelvic inflammatory disease.

All subjects were treated with a single 2 gram oral dose of metronidazole while in the physician's office. They were advised about the risk of reinfection, offered to have their partners evaluated and treated, and counseled that barrier protection should be used to protect against reinfection.

Each study subject was shown Reality™ and asked if she would use it every time she had intercourse during the study period (45 days). If she responded that she would be compliant, the subject was enrolled in the User group. If the subject felt that she would not be compliant, she was enrolled in the Control group. The User group was instructed to use Reality™ with each act of intercourse over the next 45 days. All subjects kept a diary of the number of their coital episodes.

- b. Study Population - One-hundred twenty six (126) subjects were entered into the study. Of these, 22 subjects did not satisfactorily complete the study for the following reasons: 19 (12 Controls, 7 Users) were lost to follow up; 2 Users did not have sexual intercourse during the study period; and 1 User reported that her partner used male condoms at the same time as she used Reality™. One-hundred four (104) subjects completed the study, 50 in the Control Group and 54 in the User Group.
- c. Study Results - Of the 54 study subjects who selected to use Reality™, only 20/54 (37%) reported compliant use (i.e., used Reality™ correctly during every coital act) while 34/54 (63%) reported non-compliant use. Trichomonas reinfection rates at the end of study were 7/50 (14%) for the Control Group, 5/34 (15%) in the Non-Compliant User Group, and 0/20 (0.0%) in the Compliant User Group. Although there was a lower rate of reinfection in the Compliant User Group, this difference was not statistically significant ( $\alpha=.05$ ).

6. Phase II - Pregnancy Use Effectiveness Study

- a. Study Methods - This study was conducted at nine trial sites, six in the United States and three in Latin America: Valley Center for Women's Health, Sacramento, California; Eastern Virginia Medical School, Norfolk, Virginia; Robert Wood Johnson Medical School, New Brunswick, New Jersey; Wayne State University Hospital, Detroit, Michigan; University of Arizona, Tucson, Arizona; Phoenix Baptist Medical Center, Phoenix, Arizona; Instituto de Investigación Científica, Durango, Mexico; Clínica Evangelina Rodríguez Profamilia, Santo Domingo, Dominican Republic; and Hospital General de Veracruz, Veracruz, Mexico.

Study subjects were women between the ages of 18 and 40 who were in a monogamous relationship and reported frequent sexual intercourse (>2/week). Exclusion criteria included (1) any evidence of pelvic inflammatory disease, (2) pregnancy, (3) allergy to vaginal lubricants, (4) history of toxic shock syndrome, (5) Class III or IV Pap smear within 6 months prior to entry to the study, (6) history of infertility, (7) evidence of urinary tract infection, (8) symptoms of an STD, and (9) any contraindications to becoming pregnant.

Upon entering the study, all study subjects received a pelvic examination including a chemical pregnancy test, verbal instructions on use of Reality™ and on the coital log book, and sufficient supplies of Reality™. Follow-up visits were scheduled for 1, 3 and 6 months. At the 1, 3 and 6 month follow-up visits, study subjects underwent pelvic exams and reported product use history. At the 6 month follow-up visit or at the discontinuation visit, study subjects also had a Pap smear, chemical pregnancy test and completed the acceptability questionnaire. Two weeks after the 6 month follow-up visit, study subjects were to return for an additional chemical pregnancy test. Each study subject was instructed to contact the clinic if her menstrual period was overdue or any medical problem arose.

- b. Study Population - A total of 377 women were enrolled into this study. Table 1 shows the number of women enrolled in the study, ineligible for the study and lost to follow-up for the United States (U.S.) and Latin American (L.A.) centers.

Table 1. Study Population.

Enrollment Summary	U.S. Study Subjects	L.A. Study Subjects
Total Enrolled	262	115
Lost to Follow-Up	16	2
Protocol Exclusions	21	2
Total Study Subjects	225	111

Study subjects were considered to have completed the study if (1) they returned for the 6-month follow-up visit, (2) they had not discontinued using Reality™ prior to the 6-month visit and (3) the 6-month follow-up visit occurred at least 168 days after admission. Study subjects discontinued or reached a study endpoint for the following reasons: personal, accidental pregnancy, medical reasons, planned pregnancy and lost to follow-up.

Of the 225 women enrolled in the U.S., 147 (65.3%) women completed the study without a discontinuation or endpoint event. Of the 111 women enrolled in Latin America, 47 (42.3%) completed the study without a discontinuation or endpoint event. Reasons are listed below.

Table 2. Study Subject Endpoint and Discontinuation Events.

	U.S. Study Subjects	L.A. Study Subjects
Completed Study	147 (65.3%)	47 (42.3%)
Discontinued	78 (34.7%)	64 (57.7%)
Personal Reasons	46	35
Unplanned Pregnancy	22	17
Medical Reason	4	3
Planned Pregnancy	1	4
Lost to Follow-Up	5	4
Unknown	0	1
Total	225	111

c. Study Results

1. Safety - Adverse Effects

Safety data were analyzed for all women (359) who received Reality™ and returned to the clinic for the Month 1 Visit. During follow-up, 83 women (23%) reported newly occurring medical problems or conditions (not present at admission). Many of these medical conditions were systemic in nature (cardiovascular, digestive, endocrine, musculoskeletal, nervous and respiratory systems), and probably unrelated to device usage.

The following urogenital adverse effects were reported, and may or may not be related to device usage.

- a. Changes in Cervical Cytology - Gynecological exams and Pap smears were performed on all study subjects at the initial visit, at the 6-month visit and at the final visit. During follow-up, 2 study subjects with normal Pap smears at admission had Class III dysplasia.
- b. Infections - Of the 359 study subjects, 11 (3.1%) had vaginitis (candida or monilia), 6 (1.7%) had cervicitis, 4 (1.0%) had urinary tract infections, 2 (0.6%) had cystitis, 1 (0.3%) had pelvic inflammatory disease, 1 (0.3%) had non-specific vaginitis and 1 (0.3%) had human papillomavirus infection.
- c. Irritation - One partner (0.3%) experienced irritation and erythema to the penis.
- d. Bleeding - One study subject (0.3%) reported intermenstrual bleeding/spotting.

The potential adverse effects stated above are considered acceptable for a female barrier contraceptive.

2. Effectiveness

Pregnancy rates for women using Reality™ were calculated using life table analysis. The 6-month gross cumulative life table pregnancy rates with standard error are shown in Tables 3 and 4. As seen in Tables 3 and 4, subsets of study subjects had higher 6-month gross cumulative pregnancy rates. For example, the 6-month pregnancy rate for Latin American women was 21.7% compared to 12.2% for the U.S. study subjects. The 6-month pregnancy rate for U.S. women less than 25 years of age was 21.4%. However, there were only a small number of women less than 25 years of age in the study.

Overall, there were a total of 39 pregnancies, 22 among U.S. study subjects and 17 among L.A. study subjects. Pregnancies were categorized as method or user failures by using (1) study subject's

reported history of product use during the study and (2) investigator's reported reason. Any reported non-compliance with use of Reality™ was defined as a user failure. Of the 39 pregnancies, 12 (30.8%) were attributed to methods failures; 6 due to mechanical/structure failure of the device (e.g., breakage, slippage) and 6 due to unknown causes.

The 6-month gross cumulative pregnancy rates listed in the lifetable analysis may slightly underestimate the true pregnancy rate for two reasons. First, there was a failure to discontinue several study subjects at the appropriate time in the lifetable due to infrequent sexual intercourse, as specified in the protocol. Second, a few study subjects had abnormal pelvic exams which may or may not affect their fertility. However, the effects of these protocol deviations will only slightly increase the cumulative pregnancy failure rate.

Direct statistical comparisons of the contraceptive effectiveness of Reality™ to other barrier methods, or historical controls, cannot be made for several reasons. First, there were significant differences between the study populations of historical controls and Reality™. These differences included important variables which may be associated with contraceptive use-effectiveness, for example, age and parity. Second, the study protocols differed between the historical controls and the Reality™ study.

Table 3. Gross Life-Table Pregnancy Rate for U.S. Study Subjects.

Time Months	Average at Risk	Number of Pregnancies	Monthly Failure Rate	Standard Error	Cumulative Failure Rate	Cumulative Standard Error
1	211.0	6	0.028	0.011	0.028	0.011
2	186.0	5	0.027	0.012	0.055	0.016
3	170.5	3	0.018	0.010	0.071	0.018
4	160.0	4	0.025	0.012	0.094	0.021
5	153.5	2	0.013	0.009	0.106	0.023
6	113.5	2	0.018	0.012	0.122	0.025

Table 4. Gross Life-Table Pregnancy Rate for L.A. Study Subjects.

Time Months	Average at Risk	Number of Pregnancies	Monthly Failure Rate	Standard Error	Cumulative Failure Rate	Cumulative Standard Error
1	100.0	6	0.060	0.024	0.060	0.024
2	79.0	2	0.025	0.018	0.084	0.028
3	69.0	3	0.044	0.025	0.124	0.035
4	59.0	2	0.034	0.024	0.153	0.040
5	53.5	4	0.075	0.036	0.217	0.048
6	44.0	0	0.000	0.000	0.217	0.048

Of the 225 U.S. study subjects, 86 were compliant users. A compliant user had the following characteristics: (1) never reported irregular use of Reality™, (2) did not use another method of contraception, (3) followed the instructions for use and (4) did not have fewer than four coital episodes during a month. The 6-month gross cumulative probability of a method failure among these compliant or "perfect" U.S. users is listed below.

---

Table 5. Method Failure Rate Among Compliant  
U.S Study Subjects at 6-Months.

---

Failure Rate	Standard Error
5.4	2.7

---

#### 4. Acceptability

After completion or at the time of discontinuation, study subjects and their partners completed a questionnaire on Reality™ to assess its acceptability. The most frequently noted complaints were related to not liking the inner ring and movement of the device during use. Of the 302 women who completed the questionnaire, 208 (68.9%) reported that they did not have difficulty inserting Reality™ while 94 (31.1%) reported difficulty inserting Reality™. Of the 83 women in the Treated Population who discontinued using Reality™ for personal reasons, 21 (25%) discontinued because their partner didn't like using Reality™. Approximately 17% (14 out of 83 study subjects) discontinued because they disliked the method or feared pregnancy. Of the 83 study subjects who discontinued, 8 (10%) cited discomfort as the reason for discontinuation. The acceptability of Reality™ is considered adequate for a female barrier contraceptive device.

## IX. Conclusions

The physical properties of Reality™, in terms of material strength, are adequate to meet the normal intended use of the device. The barrier properties of Reality™ with respect to sexually transmitted diseases were analyzed in an artificial, laboratory test with a very small surrogate virus (φX174). Eight devices allowed no detectable virus penetration; six allowed low level penetration, which given the test conditions, should represent insignificant virus penetration in actual use. Thus, 14 of 15 devices were significant barriers to virus penetration.

*In vitro* assays, acute animal studies and sub-chronic animal studies were performed on Reality™ to establish the safety of the device materials for their intended use. These studies revealed no evidence of cytotoxicity, dermal irritation, dermal sensitization, acute systemic toxicity or mutagenicity. Mild irritation was noted in the acute mucosal irritation test and in one of the

chronic irritation tests. A few study subjects did report irritation after using the device in the clinical investigations.

A series of clinical studies were conducted to evaluate potential adverse effects, device breakage, device displacement, acceptability, usage and comfort of the Reality™ device. These studies demonstrate that potential adverse effects, breakage, displacement and acceptability for Reality™ are adequate for its intended use.

The pregnancy use-effectiveness of Reality™ was evaluated in a single arm, multi-center clinical study for 6 months. The results of this study showed that Reality™ provided some barrier protection against pregnancy. The 6-month cumulative pregnancy rate for U.S. women was 12.2%. This rate slightly underestimates the true pregnancy rate because there was a failure to discontinue several study subjects at the appropriate time in the lifetable analysis due to infrequent sexual intercourse and a few study subjects had abnormal pelvic exams, which may affect their fertility. If these study subjects were removed from the lifetable analysis at the appropriate time, the 6-month pregnancy rate for Reality™ is expected to be approximately 13%. Because of the lack of a comparable control group, the extent of protection Reality™ provides against pregnancy compared to other barrier methods remains uncertain. The in vitro barrier properties of Reality™ combined with the pregnancy-use effectiveness data show that Reality™ should provide some barrier protection against STDs, including HIV infection, compared to using no method.

#### **X. Panel Recommendations**

The Obstetrics-Gynecology Devices Panel (the Panel) met on January 31, 1992, to consider the preliminary safety and effectiveness data on Reality™. At that time, less than one-half of the required study subjects had completed the pregnancy-use effectiveness study. At this meeting, the Panel unanimously recommended that the PMA be considered approvable subject to the submission and review of additional preclinical and clinical data, including completing the pregnancy-use effectiveness study.

On December 10, 1992, the Panel reconvened to consider the completed pregnancy use-effectiveness study and the device labeling for Reality™. Although the Panel expressed concern about the limited safety and effectiveness data and the high failure rate, the Panel voted unanimously to approve Reality™ subject to certain conditions because there is no other barrier method that women can use to protect themselves from STDs, including HIV infection, if their partners will not use latex male condoms. These conditions included the following: (1) limiting the safety and effectiveness claims, especially with respect to the prevention of HIV transmission (2) revise the patient labeling to reflect the limited data and (3) develop professional labeling. The Panel also recommended that the 12-month pregnancy rate could be estimated for Reality™ by approximately doubling the 6-month pregnancy rate.

## XI. FDA Decision

When evaluating the safety and effectiveness of Reality™, FDA considered the following relevant factors: (1) the persons for whom the device is intended; (2) the conditions of use for the device, including the conditions of use prescribed, recommended and suggested in the labeling of the device; (3) the lack of available alternatives for women whose partners do not use latex male condoms; and (4) the probable benefit to health from the use of the device weighed against any probable injury of illness from such use. FDA also considered and accepted, as a basis for approval, the use of pregnancy data as a surrogate for the prevention of STD transmission where *in vitro* tests demonstrated adequate barrier properties of the device.

Although the safety and effectiveness data were limited, FDA determined that Reality™ should provide some protection against both pregnancy and STDs, including HIV infection, for couples who do not use latex male condoms. Further, the public health benefits of some protection against HIV infection for couples not using latex condoms outweighed the limitations of available data.

In reaching this determination, FDA considered the urgent need for a means whereby women can help protect themselves from sexually transmitted diseases, including HIV infection, and the fact that the male latex condom is the only alternative. FDA also considered that couples who are currently using latex condoms, which are highly effective at preventing STDs if used properly, may choose to use Reality™ instead. Therefore, FDA determined that the labeling for the Reality™ must include a warning regarding the relative demonstrated effectiveness of the male latex condom for STD prevention compared to the limited data for Reality™. Finally, FDA considered the fact that the pregnancy-use effectiveness of Reality™ had not been tested as extensively as other new contraceptives, and that the contraceptive failure rate for Reality™ could not be statistically evaluated against one or more currently approved contraceptives, resulting in some uncertainty in the actual failure rate. However, after listening to public testimony at the December 10, 1992, Panel meeting on the need for Reality™ labeling to have a contraceptive claim to increase Reality's acceptability for use for prophylactic purposes, FDA determined that a limited contraceptive claim was in the public health interest.

Notwithstanding these issues, FDA still determined that the potential benefit of preventing HIV infection among couples who do not use latex condoms outweighed the possible risks provided that the device labeling accurately reflect the limited safety and effectiveness data. Therefore, FDA concurred with the recommendation of the Obstetrics-Gynecology Devices Panel subject to the applicant submitting additional preclinical and clinical safety and effectiveness data. The applicant amended the PMA on January 22, and 29, February 2 and 9, March 3, April 15, and May 6, 1993, to address the remaining preclinical and clinical deficiencies and revise the device labeling.

The applicant has concurred with the conditions of approval. These conditions included the following: (1) confirming the barrier properties of Reality™ by repeating the  $\phi$ X174 Bacteriophage studies on devices made from mass production lots, (2) conducting real-time aging studies to establish the device shelf-life, (3) developing professional labeling, (4) conducting focus-group studies to

refine the patient labeling, and (5) participate in future government sponsored studies of Reality™.

On-site inspection on January 25 and April 15, 1993, found the applicant's manufacturing facility to be in compliance with the device Good Manufacturing Practice Regulations.

FDA has determined that, based on data submitted in the PMA, there is reasonable assurance that Reality™ is safe and effective for its intended use, and issued an approval order on MAY 7 1993.

## XII. Approval Specification

Directions for Use: See the Labeling (Attachment 1).

Warning, Hazards to Health for Use of the Device: See indications, contraindications, warnings, precautions and adverse effects in the labeling (Attachment 1).

Post-Approval Requirements and Restrictions: See approval order (Attachment 2).

A copy of the final labeling and all subsequent changes to the labeling approved by CDRH may be reviewed at the Food and Drug Administration, Center for Devices and Radiological Health, 1390 Piccard Drive, Rockville, Maryland 20850.

## References

- 1 National Toxicology Program, "Carcinogenesis Studies of 4,4'-Methylenedianiline Dihydrochloride (CAS No. 13552-44-8) on F344/N Rats and B6C3F<sub>1</sub> Mice (Drinking Water Studies" Technical Report No. 248, 1983.
- 2 The United States Pharmacopeia, USP XXII.
- 3 Gad, S.C. and C.P. Chengelis (Eds). "The Guinea Pig" in *Animal Models in Toxicology*, Marcel Dekker, New York, 1992.

Attachment 1

## REVISED LABELING FOR REALITY™ THE FEMALE CONDOM

The following statement will appear prominently on the carton and device package. It will also appear prominently (highlighted or in a box) as the first statement on the instructions for use.

### "KEY ELEMENT"

#### Important Information:

- Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly.
- If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.
- Reality only works when you use it. Use it every time you have sex.
- Before you try Reality, be sure to read the directions in the box and learn how to use it properly.

A. Package Insert/Instruction Leaflet\*

Important Information:

- Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly.
- If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.
- Reality only works when you use it. Use it every time you have sex.
- Before you try Reality, be sure to read the directions in the box and learn how to use it properly.

REALITY™ Female Condom

Reality is intended to be worn by women during sex. It can help prevent pregnancy and sexually transmitted diseases, including AIDS (HIV infection).

Because Reality is new, it may look different to you or you may feel nervous about trying to insert it -- similar perhaps to how you felt the first time you inserted a tampon, or a diaphragm. After you become used to Reality, it should become easier and more comfortable to use.

It's important to practice putting Reality in without having sex. Take your time. Get familiar with Reality's different shape and the way it looks. See how it hangs outside the vagina when in place.

1. Product Overview

a. Description

Reality is a soft, loose-fitting plastic pouch that lines the vagina. It has a soft ring at each end. The ring at the closed end is used to put the device inside the vagina and holds it in place. The other ring stays outside the vagina and partly covers the lip area.

Use a new Reality with each sex act. If you use it again, do not expect it to protect you. Use a new Reality every time you have sex.

b. Precautions

Here are some important things to remember in order to get the best protection from Reality:

- (1) Use Reality every time you have sex. If Reality is not used every time, your risk of becoming pregnant or getting a sexually transmitted disease will be higher.
- (2) Use a new Reality with each sex act. If you use it again, do not expect it to protect you.
- (3) Do not remove Reality's inner ring. This ring helps keep the device in place during use. If you remove the ring, Reality will not work as well.
- (4) Do not use Reality and a male condom at the same time. If you do, both products will not stay in place.
- (5) Don't tear Reality. Be careful of sharp objects, like rings or jagged fingernails. If Reality should tear, remove it and use a new one.
- (6) Use more lubricant if needed. If the device comes out of the vagina during use, or if the outer ring gets pushed inside, use a new Reality. Also, add some extra lubricant. You can put the lubricant either inside the device or on the man's penis. The added lubricant may also make Reality more comfortable to use and may allow the penis to slip easily in and out of the vagina.

c. About Reality's Effectiveness

How Reality was tested

Limited laboratory tests showed that Reality can block the germs that cause sexually transmitted diseases. Reality was only tested in humans for its ability to prevent pregnancy. That's because researchers did not want to take a chance on exposing people in the tests to AIDS and other sexually transmitted diseases. The idea was that if Reality can prevent sperm from entering the woman and causing pregnancy, it can also prevent spreading the germs that cause sexually transmitted diseases.

Reality was tested for use over 6 months in U.S. women. This was not as long and did not include as many woman as other contraceptive studies. The study shows Reality provides protection against pregnancy. The pregnancy rate in the 6-month study was 13%. The estimated 1 year pregnancy rate for Reality ranges from 21% to 26%. This means that about one in four women who use Reality may become pregnant during a year. Couples who used Reality correctly with every sex act had a lower pregnancy rate.

This table shows the overall pregnancy rates from studies of barrier contraceptives. Depending on if you use the method correctly every time you have sex, your risk of pregnancy may be higher or lower. Other contraceptive products not listed here, such as birth control pills, are more effective at preventing pregnancy.

"KEY ELEMENT"

Overall Pregnancy Rates for Barrier Contraceptives

Condoms Which Protect Against Pregnancy and Sexually Transmitted Diseases

	<u>Pregnancy Rates**</u>	
	<u>6 Months</u>	<u>1 Year</u>
Reality Female Condom*	13%	26%
Male Latex Condom <sup>1</sup>	8%	15%

Pregnancy Rates with Other Methods

	<u>Pregnancy Rates**</u>	
	<u>6 Months</u>	<u>1 Year</u>
Cervical Cap	10%	18%
Diaphragm	8%	15%
Sponge	12%	17%

	<u>Pregnancy Rates</u>
	<u>1 Year</u>
Unprotected sex <sup>2</sup>	85%

\* Yearly failure rates for Reality were estimated by doubling the 6-month pregnancy rate.

\*\* Pregnancy rates for Reality, Cervical Cap, Diaphragm and Sponge are from clinical trials. Actual use failure rates may be higher or lower.

<sup>1</sup> 1988 National Survey of Family Growth.

<sup>2</sup> Trussell, et.al., Studies in Family Planning 21(1), Jan/Feb 1990.

Remember - Reality can only work if you use it. Also remember - if you are trying to prevent sexually transmitted diseases - there is no "safe" time when you can have sex without protection. Use Reality every time you have sex.

If you must not become pregnant because of a medical condition, talk to your doctor or family planning clinic before using any contraceptive.

d. When to Use Reality

Reality can be inserted up to 8 hours before sex. However, most women insert Reality between 2 to 20 minutes before sex.

Reality should be removed after sex and before you stand up. It is for one-time use. Use a new Reality with each sex act.

2. Problems using Reality - Some women have reported problems using Reality. One of the problems is the outer ring can be pushed inside the vagina during sex. Some women have also reported that the penis slipped to the side of the device on entering the vagina. Other problems included difficulty inserting Reality, minor irritation, discomfort and breakage.

3. Storage Instructions

Store Reality at normal room temperature. Do not use Reality after its expiration date because it will not work as well.

SOME FEATURES OF USING REALITY

- You can insert Reality yourself. It gives you a way to protect yourself.
- Reality warms up as soon as you insert it. It is both strong and soft.

## INSTRUCTIONS FOR USE

### To Open the Packet

- Pull the two sides of the packet apart from the center of the top.
- Take out Reality and look at it closely.
- Rub the outside of the pouch together to be sure the lubrication is evenly spread inside.
- To add more lubricant, simply give one quick squeeze of the extra lubricant. Try different amounts to see what's best for you and your partner. Try starting with 2 drops.

### To Insert Reality

- Find a comfortable position. Try standing with one foot up on a chair, or sit with knees apart, or lie down.
- Be sure the inner ring is at the bottom, closed-end of the pouch.
- If you wish, add a drop of extra lubricant to the closed-end outside tip of the pouch or to the outside ring before you insert Reality.
- Hold the pouch with the open end hanging down. While holding the outside of the pouch, squeeze the inner ring with your thumb and middle finger.
- Place your index finger between the thumb and middle finger and keep squeezing the inner ring. FIG. C.

- Still squeezing Reality with your three fingers, with your other hand, spread the lips of your vagina and
- Insert the squeezed Reality as shown in FIG. D.

Take your time. If Reality is slippery to insert, let it go and start over.

- Now push the inner ring and the pouch the rest of the way up into the vagina with your index finger. CHECK TO BE SURE THE INNER RING IS UP JUST PAST THE PUBIC BONE. Look at FIG. E. You will feel the pubic bone by curving your index finger when it is a couple of inches inside the vagina. (Please label the pubic bone on the diagram.)

This step may be hard to do on the first or second try because Reality is lubricated.

Take your time and push Reality up to where you can feel the bone.

Make sure Reality is inserted straight (not twisted) into the vagina. It is also important that the OUTSIDE RING LIES AGAINST THE OUTER LIPS AS SHOWN IN FIG. F.

About one inch of the open end will stay outside your body. See FIG. F. While this may look unusual, this part of Reality helps protect you and your partner during sex. Once the penis enters, the vagina will expand and the slack will decrease.

Until you and your partner become comfortable using Reality, use your hand to guide the penis into the pouch. See FIG G.

After two or three times, you should become familiar with

using Reality and should hardly notice the sheath or the outer ring during sex. For added comfort, you may want to add more lubricant either inside or outside Reality. Some couples like to add extra lubricant directly to the penis.

#### During Intercourse

You may notice that Reality moves around during sex. See FIG. H.

- Movement side-to-side of the outer ring is normal.
- Sometimes Reality may slip up and down in the vagina, "riding" the penis. If you notice Reality is slipping, add lubricant to the penis or inside the pouch.
- If you begin to feel the outer ring being pushed into the vagina, STOP. See figure x. If the penis starts to enter underneath or beside the sheath, STOP. See figure y. Take out Reality. Put it in a new Reality, and add extra lubricant to the opening of the pouch or on the penis. Make sure the outside part lies over the lip area.

### After Intercourse

To take out Reality, squeeze and twist the outer ring to keep the sperm inside the pouch. Pull out gently. Throw away in a trash can. Do not flush. Do not reuse. FIG. I.

### Remember

To help reduce your risk of pregnancy and spreading or getting a sexually transmitted disease:

- Use a new Reality every time you have sex.
- Follow the directions carefully.
- Be sure you don't tear the sheath with fingernails or other sharp objects.
- Use enough lubricant.

## Questions You May Have About the Proper Use of Reality

### 1. WILL REALITY ALWAYS PROTECT AGAINST PREGNANCY AND STDs?

No method is 100 percent effective. Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly. If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.

### 2. HOW DO I KNOW WHEN REALITY IS UP FAR ENOUGH?

Using your index finger, push the device so that the lower ring of the device is against the pubic bone. You will find the pubic bone by curving your index finger when it is a couple of inches inside the vagina.

### 3. WHAT DO I DO IF THE OUTER RING IS PUSHED INSIDE THE VAGINA?

STOP. Remove the Reality device. Insert a new Reality according to the directions. Add extra lubricant to inside the device at the opening of the vagina. Consider lubricating the penis also. This problem can occur if there isn't enough lubricant, or if the inner ring isn't in the proper position.

### 4. WILL REALITY BE NOISY DURING SEX?

If properly lubricated, there should be little noise. If you experience noise during sex, add extra lubricant.

### 5. WHAT IS THE PURPOSE OF THE LUBRICANT?

The lubricant helps the penis move freely in and out, prevents

slipping, and discomfort. If the penis does not slip in and out easily, add more lubricant.

6. WILL I FEEL REALITY ONCE IT IS IN PLACE?

Some people may feel Reality and some may not if it is properly in place and lubricated.

7. WHAT DO I DO IF THE PENIS IS INSERTED OUTSIDE THE POUCH?

STOP. Remove the penis. Insert a new Reality and make sure the outer ring lies flat over the lip area. When you reinsert the penis, guide it with your hands. Do not let the penis directly touch the vagina.

8. WILL REALITY RIP OR TEAR WHILE I AM USING IT?

Studies show that Reality rips or tears less than 1% of the time. If you think Reality has been ripped or torn, remove it right away, throw it away, and insert a new Reality.

9. WILL REALITY BUNCH UP INSIDE THE VAGINA?

Reality should not bunch up inside if it is inserted right and if there is enough lubricant. If you feel the outer ring begin to slip inside, STOP. Remove the Reality device. Insert a new Reality device according to the directions. Add extra lubricant inside the device at the opening of the vagina.

12. WHAT DOES THE OUTER RING FEEL LIKE DURING SEX?

While aware that the outer ring is there, most women say that once they become comfortable with how it looks, they forget about it and don't feel it during sex.

13. WHAT DO I DO IF REALITY DOES NOT STAY IN PLACE DURING SEX?

If Reality moves down the vagina causing discomfort, either push it back up or remove Reality. If you push it back up, add lubricant. If you remove Reality, use a new one and add extra lubricant.

- Latex condoms for men are highly effective at preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly.
- If you are not going to use a male latex condom, you can use Reality to help protect yourself and your partner.

DO YOU HAVE A QUESTION ON  
HOW TO USE REALITY?  
CALL your doctor or family planning clinic  
or  
CALL 1-800-XXX-XXXX

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

JUN 8 1993

Food and Drug Administration  
Center for Devices and  
Radiological Health  
1390 Piccard Drive  
Rockville, Maryland 20850

May 26, 1993

MARY ANN LEEPER  
WISCONSIN PHARMACAL COMPANY  
919 N. MICHIGAN AVENUE  
SUITE 2208  
CHICAGO, IL 60611

PMA Number: ~~P910064~~ SUP 001  
Letter Dated: 05/25/93  
Received: 05/26/93  
Product: REALITY(TM) VAGINAL  
POUCH

Dear MS. LEEPER:

The Center for Devices and Radiological Health (CDRH) acknowledges its receipt of the premarket approval application (PMA) supplement submitted by you for the above referenced device. This PMA supplement has been assigned an unique document control number. Failure to reference this supplement number in further correspondence may result in processing delays.

The Federal Food, Drug, and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, states, in section 522(a)(1), that if your device is a permanent implant the failure of which may cause death, you may be subject to required postmarket surveillance. If your PMA or PMA supplement is approved after November 8, 1991, and your device is an Aneurysm Clip, Annuloplasty Ring, Artificial Embolization Device, Automatic Implanted Cardioverter Defibrillator System, Cardiovascular Intravascular Filter, Cardiovascular Permanent Pacemaker Electrode (lead), Central Nervous System Fluid Shunt, Coronary Vascular Stent, Implantable Pacemaker Pulse Generator, Implanted Diaphragmatic/Phrenic Nerve Stimulator, Intracardiac Patch or Pledget, Intravascular Occluding Catheter, Replacement Heart Valve, Total Artificial Heart, Tracheal Prosthesis, Vascular Graft Prosthesis (less than 6 mm diameter), Vascular Graft Prosthesis (6 mm or greater diameter), Vena Cava Clip, or Ventricular Assist Device - Implant, you will be subject to the required postmarket surveillance and so notified in your final approval order. This list is subject to change without notification. If you have any questions as to whether or not your device may be subject to post-market surveillance or about this program, please contact the Postmarket Surveillance Studies Branch at (301) 227-8639.

All further correspondence shall be referred to as amendments to the PMA supplement, and the required number of copies bearing the above PMA supplement number shall be submitted directly to:

Food and Drug Administration  
Center for Devices and  
Radiological Health  
PMA Document Mail Center (HFZ-401)  
1390 Piccard Drive  
Rockville, Maryland 20850

You will be notified of any need for additional information and the CDRH filing decision. Questions concerning this submission may be directed to the PMA Staff at (301) 427-1186 or to the reviewing division within the CDRH Office of Device Evaluation.

Sincerely yours,

*151 Michael Gentry*

Charles H. Kyper  
Director, Premarket Approval Staff  
Office of Device Evaluation  
Center for Devices and  
Radiological Health



PREMARKET APPLICATION (PMA) FOR  
THE REALITY VAGINAL POUCH  
(WPC-333, Female Condom)

Related Documents:

Master File - 292

510(k) - K890316

IDE - Use-Effectiveness	G890203
Vaginal Trauma	G890229
Instructions for Use	G900001
Anal Intercourse	G900066
Reinfection Rate Study	G900114

Indication for Use:

Reality is intended to be used by women as a barrier device to protect against AIDS, and other sexually transmitted diseases (STDs), and unintended pregnancy.

Manufacturing Site:


Reality will be manufactured at Wisconsin Pharmacal headquartered in Jackson, Wisconsin 53037.

Wisconsin Pharmacal will be ready for inspection, November 1, 1991.

Environmental Impact:

Wisconsin Pharmacal claims categorical exclusion. There will be no significant increase in the total quantities of thermoplastic polyurethanes or their manufacturing waste products or effluents distributed into the environment, either as waste water, waste materials, or air emissions.

Submitted by:

  
Mary Ann Leeper, Ph.D.  
Director of Development

Food and Drug Administration  
Center for Devices and  
Radiological Health  
1390 Piccard Drive  
Rockville, Maryland 20850

October 24, 1989

FAMILY HEALTH INTERNATIONAL  
P.O. BOX 13950  
RESEARCH TRIANGLE PARK, NC 27709  
ATTN: WILLIAM L. HUNT

Dear Sponsor:

The information you have submitted, as required by the Food and Drug Administration (FDA) investigational device exemptions (IDE) regulation, has been assigned the following document control number:

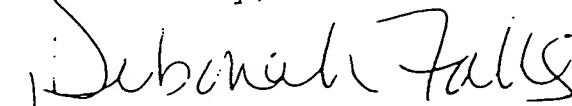
IDE Number: G890203  
Dated: 10/17/89  
Received: 10/24/89  
Device: WPC-333, VAGINAL POUCH

FDA will notify you when the review of this submission has been completed or if any additional information is required. In accordance with Section 812.30 of the IDE regulation, you may begin your investigation 30 days after the date FDA received your submission, unless FDA notifies you that your investigation may not begin.

Any administrative questions concerning this submission should be directed to the IDE staff at (301) 427-1190. Any future correspondence regarding this submission should be identified with your IDE number and should be submitted, in triplicate, to:

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Document Mail Center (HFZ-401)  
1390 Piccard Drive  
Rockville, Maryland 20850

Sincerely,

  
Nancy Faust Teague  
Director, IDE Staff  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

## Memorandum

OCT 25 1989

General Program Memorandum #G89-2

From Director  
Office of Device Evaluation(HFZ-400)

Subject IDE/PMA Expedited Review Process

To ODE Review Staff

Purpose.

Occasionally a new device will be developed for application to a life-threatening or severely debilitating illness for which there is no alternate diagnosis, therapy, or prevention modality. It may be in the interest of the public health to make these devices available in an expedited manner without compromising major safety and effectiveness criteria. This guidance is intended to expedite the development, evaluation and marketing of new devices intended for use in life-threatening or severely debilitating illnesses, especially where no satisfactory alternate exists. This program is intended to parallel the expedited drug review program for CDER. Except as noted below, documents under expedited review are subject to all other controls and requirements applicable to comparable documents.

Background.

Physicians and patients are generally willing to accept greater risks or side effects from devices that are life-supporting or life-sustaining and applied to life-threatening or severely debilitating illnesses. The benefits of the device need to be evaluated in light of the severity of the disease and the lack of satisfactory alternative modalities.

A "life-threatening" disease is defined as one in which the likelihood of death is high unless the course of the disease is interrupted. This includes any disease whose progression is likely to lead to death in a short period of time, e.g., in less than one year.

"Severely debilitating" is defined as a condition or disease which leads to major irreversible morbidity. Proposed studies may examine the device's capacity to prevent or reverse what would otherwise be irreversible damage.

When the end points of a clinical study relate to survival or prevention of major irreversible morbidity, it is imperative that the initial controlled clinical trials be well designed, closely monitored, and conducted in a scientifically valid manner. In this way, the true merit of the device can be evaluated as promptly as possible.

2  
The implementation of an expedited review program for devices may require setting priorities such that those expedited reviews are given precedence over routine reviews.

### Procedure.

The success of this program is contingent upon timely communications and ongoing dialogue between sponsors and CDRH staff. Since these devices will directly impact the treatment of life-threatening and/or severely debilitating diseases, it is expected that the devices will be investigated under an approved investigational device exemption (IDE) and marketed through the premarket approval (PMA) process. The premarket notification (510(k)) process may be appropriate for some of these devices.

#### A. Pre-IDE Meetings

Center staff will be available to meet with sponsors prior to the submission of an IDE to consult on the design of the initial clinical studies and to review the preclinical data. Advisory panel members may be consulted as necessary.

#### B. Feasibility IDE

The Center has issued guidance concerning IDE applications for feasibility studies involving limited numbers of human subjects. See IDE Memorandum #D89-1, Review of IDEs for Feasibility Studies, dated May 17, 1989. In this way, limited initial clinical studies may be performed to evaluate a new device entity or design concept.

#### C. Meetings During Clinical Investigations

Center staff will monitor reports of the progress of the IDE clinical studies and evaluate the data with the special purpose of ascertaining if sufficient and appropriate data are available to support a PMA submission. Advisory panel members may be consulted when appropriate.

#### D. PMA Consultation Meeting

The Center will advise the sponsor concerning the necessary elements and data to be presented in a PMA submission to document safety and effectiveness of the device. The Center will attempt to realistically balance the risks versus the benefits of the device in formulating its requirements for the pre-clinical studies required for their approval. Continued subject entry into an investigation under the IDE may occur while the PMA is under review. The current routine administrative procedures will be followed in coming to a decision of approvability.

#### E. Post-market Studies

Where the PMA submission contains minimal scientific and clinical data, the sponsor will likely be required to conduct certain follow-up or

6. 2. 7-7  
Additional post-approval studies in order to obtain a complete understanding of the device's safety and effectiveness.

#### F. Guidance Documents

CDRH staff will prepare and issue guidance documents as needed for specific device categories to facilitate preclinical and clinical trial designs and the preparation of PMA submissions.

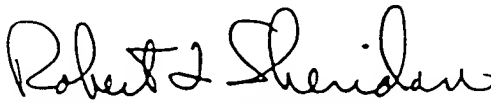
#### Implementation

A device may be recommended to the Center for Devices and Radiological Health for expedited review consideration by any interested individual or organization. After due consideration is given to the nature of the device, the targeted illness, the availability of alternative therapeutic, diagnostic, and preventative modalities, and the potential benefit of the device, the Office of the Director, ODE, will determine if the device qualifies for an expedited review.

For those devices designated for expedited review, each division will enter them into a separate log designated "Expedited." The division director will make weekly status reports of all expedited submissions to the Director, ODE.

#### Effective Date.

This policy is effective immediately.

  
Robert L. Sheridan

NOV 22 1989

Food and Drug Administration  
8757 Georgia Avenue  
Silver Spring MD 20910

Roberto Rivera, M.D.  
Director, Clinical Trials Division  
Family Health International  
P.O. Box 13950  
Research Triangle Park, North Carolina 27709

Re: G890203  
Reality<sup>TM</sup> - Intravaginal Pouch  
Dated: October 17, 1989  
Received: October 24, 1989

Dear Dr. Rivera:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. We regret to inform you that your application is disapproved and you may not begin your investigation. Our disapproval is based on the following deficiencies:

#### PRECLINICAL INFORMATION

##### Material Chemistry

1. Provide information to demonstrate that the polyurethane membrane is stable under the proposed conditions of use and that it does not release toluendiisocyanate (TDI) or 2,4-Toluenediamine (TDA). Provide a comprehensive carcinogenic risk assessment for TDI and TDA leachables. If no leachables are detected, provide the assessment based on the detection limits of your test.
2. Provide the results of studies to demonstrate that there is no chemical interaction between the silicone lubricant and the polyurethane components of the intravaginal pouch.

##### Material Toxicology

3. Clarify whether the devices tested in the battery of biocompatibility tests, described in the master file, were lubricated or unlubricated.
4. Provide information on the acute systemic toxicity and muscle implantation effects of the device material. The master file does not contain this required information.

##### Physical Properties

5. Clarify whether the devices tested in the battery of physical tests, described in the master file, were lubricated or unlubricated.

Page 2 - Dr. Roberto Rivera

6. Provide justification that the colital model (used in the permeability study described in the master file) will give adequate information on permeability. Provide full details of this model, including its design, component materials and properties, and dimensions. This description should include diagrams to illustrate its performance. Provide all methodological details. Demonstrate the reproducibility of this test. Using this test, compare the permeability of your device material to that of the condom.

The permeability study uses the cytomegalovirus (CMV) and the human immunodeficiency virus (HIV) as test probes to demonstrate permeability. However, the molecular size of CMV and HIV do not represent the full range of sizes of microbiological organisms of sexually transmitted diseases (STDs). Specifically, the HIV and CMV probes are 3 to 4 times larger than the hepatitis B antigen, another STD agent. Provide justification for studying only HIV and CMV.

#### Shelf-Life

7. Provide the results of testing for shelf-life to show that the chemical formulation and important material properties, such as tensile strength and permeability, are unaffected by aging. This testing should be conducted on devices that were packaged with the intended lubricant. Results from this testing should be used to determine the expiration date for investigational samples used in your Phase I and Phase II clinical studies.
8. Provide tensile data for the "0" day and 1 month for the dry and silicone lubricant environment, as well as the "0" day data for the water-based lubricant environment. For the purposes of comparison, provide 6-month data for the water-based lubricant. Provide tensile stress at 100, 200, and 300 % elongation and the ultimate elongation at break for all groups at all time periods and temperatures. Determine the modulus.

#### CLINICAL INFORMATION

##### Feasibility Studies (Phase I)

9. The device master file describes four clinical studies of your device. These studies, however, do not address potential adverse effects that may be attributable to device use. Provide results from a small feasibility study to demonstrate the safety of this device. This study should be conducted pursuant to that agreed in our October 12, 1989 meeting with your firm and the manufacturer (minutes of meeting enclosed). Documentation should include Papanicolaou (PAP) smears and cervical photographs.

Page 3 - Dr. Roberto Rivera

10. The first clinical study described in the master file (Study 1 - Appendix A-7) shows device slippage, outer ring inside the vagina, and the device "carried out" of the vagina with the penis a total of 30.7 % of the coital episodes. The next clinical study described in the master file (Study 2 - Appendix A-8) shows that, in 17.7 % of the evaluated coital episodes, your device came out of place by the outer ring entering the vagina. Another study (Study 3 - Appendix A-9) shows that the device "fell out" or the outer ring was "pulled in" 14.8% of the time. The only other clinical study that addresses device displacement and/or expulsion (Study 4 - Appendix A-10) shows that this occurred 15 times in 76 coital episodes (19.7 %). Provide justification for proceeding to a larger clinical study when all of your preliminary studies show such a high device failure rate.
11. The feasibility study must also provide information demonstrating that a woman can easily understand and follow written instructions for use of your device. This study must then be used to improve the instructions for use that will be used in your Phase II study.

Before proceeding to your proposed Phase II clinical study, conduct a Phase I feasibility study of the device to answer the above questions.

If you submit information correcting the deficiencies, we will reevaluate your application. The information should be identified as an IDE amendment referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

We must inform you that you have an opportunity to request a regulatory hearing regarding our disapproval of your IDE application. Procedures governing any such hearing are described in the enclosure "Procedures to Request a Regulatory Hearing."

You should give serious consideration to the following items which are considered essential for the analysis of your data for the purposes of determining safety and effectiveness of a future premarket approval (PMA) application. Although you may not proceed to your Phase II study until you have satisfactorily responded to our questions on the preclinical and Phase I studies, the following are preliminary review comments on your proposed Phase II study.

- 1) Provide justification for this device to qualify for an expedited approval process per FDA's draft premarket testing guidelines (copy enclosed), in light of the device slippage, displacement, and expulsion rates found in your preliminary studies.

Page 4 - Dr. Roberto Rivera

2) Phase II study

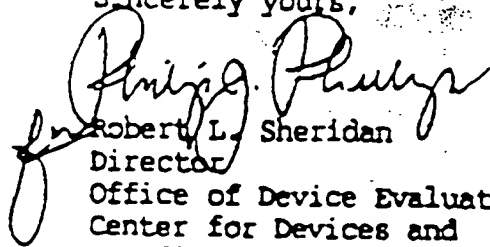
- a. Clarify the statement "Center-by Treatment interaction", given on p. 77 of the IDE application.
- b. Justify your expected 40% drop-out rate for a clinical study that will be of six-months duration.
- c. Justify your assumed study outcome of 12 pregnancies per 100 woman-years. Clarify whether this includes "method failure pregnancies", "user failure pregnancies", or both.

3) Instructions for Use

The Phase II study must incorporate a subgroup study to demonstrate that women with limited education and/or literacy can follow instructions. This study must demonstrate, as an extension of the results from the Phase I studies, how well patients will understand printed instructions (for either an OTC or prescription device) and how well patients will understand a health care provider's instructions (for a prescription device).

If you have any questions, please contact Raju G. Kammula, D.V.M., Ph.D., at (301) 427-1180 or Nancy F. Teague, at (301) 427-1190.

Sincerely yours,

  
Robert L. Sheridan  
Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosures

TO: Wisconsin-Pharmaceutical (District of Agency)

FROM: FDA/CDRH/ODE/DOED

TELEPHONE: 427-1180

ATTENTION: Mary Ann Leeper

Number of pages: 4 (including coversheet)

FROM: Raju Kammula

Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Device Evaluation  
10 Piccard  
Piccard Building  
Rockville, MD 20850

Fax Machine: (301) 427-1977

Confirmation Number: (301) 427-

## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

JAN 12 1990

William L. Hunt, Ph.D.  
Family Health International  
P.O. Box 13950  
Research Triangle Park, North Carolina 27709

Re: G890203/A2  
Reality<sup>TM</sup> - Intravaginal Pouch (WPC-333): Phase II Clinical Study  
Dated: December 14, 1989  
Received: December 15, 1989

Dear Dr. Hunt:

The Food and Drug Administration (FDA) has reviewed the amendment to your investigational device exemptions (IDE) application. Your application is conditionally approved. You may begin your investigation at the following institutions, using a revised informed consent document as described below, after you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA. Your investigation is limited to 7 institutions and 350 subjects.

Eastern Virginia Medical School  
Norfolk, Virginia

University of Arizona  
Tucson, Arizona

Wayne State University/Hutzel Hospital  
Detroit, Michigan

Valley Center for Women's Health  
Sacramento, California

This approval is being granted on the condition that, within 30 days from the date of this letter, you submit information correcting the following deficiencies:

1. The patient informed consent form must contain the following elements per 21 CFR 50.25:
  - a. a disclosure of appropriate alternatives, including other barrier contraceptive devices;
  - b. a description of any reasonable foreseeable risks or discomforts to the subject, including sensitization, irritation, and vaginal, cervical, or pelvic changes; and
  - c. the anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (Your present statement is vague and requires clarification.)

Page 2 - William Bunt, Ph.D.

2. Besides the immediate package containing the Reality™ device, the instruction manual must also contain the following statement on the front cover: "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

If you do not provide this information within 30 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of IRB approval for the addition of investigational sites (21 CFR 812.35(b)) provided:

1. The total number of investigational sites does not exceed seven.
2. You maintain current records on:
  - a. the names and addresses of all investigational sites,
  - b. the names and addresses of all investigators and identifying those that are currently participating,
  - c. the names, addresses and chairpersons of all IRBs,
  - d. the dates of IRB approvals, and
  - e. the dates of first shipments or first use of investigational devices for all participating institutions.
3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.
4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.
5. You submit to FDA, within 2 days of receipt of a request by FDA, a current list containing the information specified in 2(a-e) above.
6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has approved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. You must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation

Page 3 - William L. Bunt, Ph.D.

past the limit specified above. If you do not agree to these conditions, you must comply with the full requirements of submission of a supplemental IDE application for new investigational sites (21 CFR 812.35(b)). FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement.

We would like to point out that FDA approval of your IDE application does not imply that this investigation will develop sufficient data to assure a determination of substantial equivalence of a premarket notification (510(k)) submission or sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers Assistance at their toll free number (800) 638-2041 or (301) 443-6597.

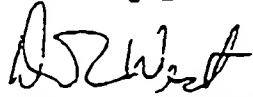
You should also give serious consideration to the following item which are considered essential for the analysis of your data for the purpose of determining safety and effectiveness for a future PMA application:

The data submitted to demonstrate the permeability characteristics of the Reality<sup>TM</sup> device with respect to sexually transmitted viruses may not be adequate to support premarket approval under FDA's proposed expedited pathway. Draft guidelines addressing this aspect will soon be published in the Federal Register as a Notice of Availability. We will also provide you, upon request, with a study protocol used in our laboratory to study such effects.

We have enclosed the guidance document entitled "Sponsor Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Please contact the individuals listed below if you have any questions regarding these responsibilities.

If you have any questions, please call Raju G. Kammula, D.V.M., Ph.D., at (301) 427-1180 or Nancy F. Teague, at (301) 427-1190.

Sincerely yours,

  
(8) Robert L. Sheridan  
Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

MAR 8 1990

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

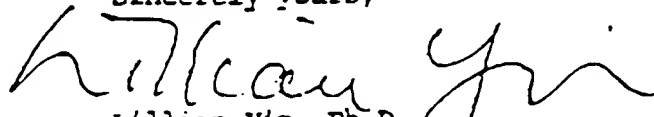
Family Health International  
Attn: William L. Hunt, Ph.D.  
P. O. Box 13950  
Research Triangle Park, North Carolina 27709

Re: G890203/S1  
REALITY<sup>TM</sup> Intravaginal Pouch  
Dated: February 6, 1990  
Received: February 12, 1990

Dear Dr. Hunt:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application. You have corrected the deficiency listed in our January 12, 1990 conditional approval letter. Therefore, your application is approved and you may conduct your investigation at the institution listed in our January 12, 1990 letter after you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA. Your investigation is limited to 7 institutions and 350 subjects.

Sincerely yours,

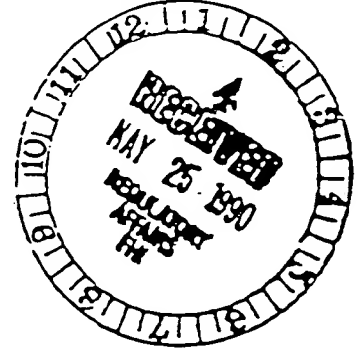


Lillian Yin, Ph.D.  
Director, Division of OB-GYN, ENT  
and Dental Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

MAY 22 1990

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

William L. Hunt, Ph.D.  
Director  
Regulatory Affairs Division  
Family Health International  
P.O. Box 13950  
Research Triangle Park, North Carolina 27709



Re: G890203/S2  
Reality<sup>TM</sup> - Intravaginal Pouch (WPC-333): Phase II Clinical Study  
Dated: April 25, 1990  
Received: May 1, 1990

Dear Dr. Hunt:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing the addition of two additional institutions to increase the number of sites from 7 to 9. Your supplement is approved and you may begin your investigation at the institutions after you have obtained institutional review board (IRB) approval. Your investigation is limited to nine institutions and 350 subjects. FDA acknowledges that 3 institutions have received IRB approval and include:

Eastern Virginia Medical School  
Norfolk, Virginia

University of Arizona  
Tucson, Arizona

Valley Center for Women's Health  
Sacramento, California

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of IRB approval for the addition of investigation sites (21 CFR 812.35(b)) provided:

1. The total number of investigation sites does not exceed 9.
2. You maintain current records on:
  - a. the names and addresses of all investigational sites,
  - b. the names and addresses of all investigators, and identifying those that are currently participating,
  - c. the names, addresses and chairperson of all IRBs,
  - d. the dates of IRB approvals, and
  - e. the dates of first shipments or first use of investigational devices for all participating institutions.
3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.
5. You submit to FDA, within 2 days of receipt of a request by FDA a current list containing the information specified in 2(a-e) above.
6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has improved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. You must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation past the limit specified above. If you do not agree to these conditions, you must comply with the full requirements of submission of a supplemental IDE application for new investigational site (21 CFR 812.35(b)). FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement.

FDA has also reviewed your proposed changes in the investigational plan and informed consent document. Your request for changes in the investigational plan, identified as 1, 2, and 4 - 8 and the changes in the informed consent document (reference: Proposal 956 - Amendment 1, three pages) are approved, and you may implement those changes at the institutions identified above and at new institutions that meet the requirements above.

We regret to inform you that your request to amend exclusion criterion number 10 with the addition of the sentence, "Volunteers with Pap smears that have cellular changes associated with HPV but do not indicate dysplasia may be admitted into the study," (proposed change number 3) is disapproved and you may not implement this change in your investigational plan. Our disapproval is based on the Human Papilloma Virus (HPV) being a sexually transmitted disease (STD) which presents significant risk to the study subjects and that its presumed presence, suspected by "cellular changes associated with HPV" may either mask a change in a subject's Pap smear due to the device or may exacerbate a change in a subject's Pap smear. If you submit information justifying the addition of this as an exclusion (inclusion) criterion, FDA will reevaluate this proposed change in the investigational plan. This information should be identified as an IDE supplement referencing the IDE number, and must be submitted in triplicate to:

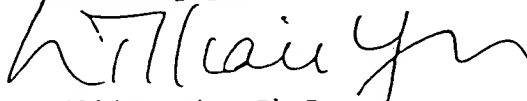
IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1390 Piccard Drive  
Rockville, Maryland 20850

Page 3 - William L. Hunt, Ph.D.

We must inform you that you have an opportunity to request a regulatory hearing regarding our disapproval of your IDE supplement. Procedures governing any such hearing are described in the enclosure "Procedures to Request a Regulatory Hearing."

If you have any questions, please contact Raju G. Kammula, D.V.M., Ph.D., at (301) 427-1180 or Nancy F. Teague at (301) 427-1190.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Lillian Yin".

Lillian Yin, Ph.D.  
Director, Division of OB/GYN, ENT  
and Dental Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

Enclosure

PROCEDURES TO REQUEST A REGULATORY HEARING

In order to request a regulatory hearing regarding FDA's disapproval or proposed withdrawal of approval of your IDE application, you are required to file the request within 30 days from the date of FDA's letter stating such decision. If FDA has not received from you a request for a hearing within that time, you will be considered to have foregone the opportunity to request a hearing and no hearing will be held. Any request for a hearing may be filed by mail, telegram, telex, personal delivery, or any other written mode of communication, and addressed to the following person:

Warren Howard  
Division of Regulations Policy (HFC-220)  
Office of Regulatory Affairs  
Food and Drug Administration  
5600 Fishers Lane, Room 12A-17  
Rockville, MD 20857  
(301) 443-3480

This notice of an opportunity for a regulatory hearing and any hearing on FDA's disapproval or proposed withdrawal of approval of the IDE application is governed by 21 CFR, Part 16, and section 201(y) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(y)).

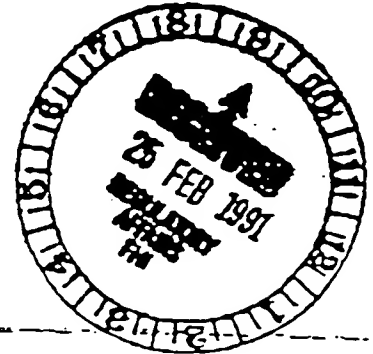
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
1390 Piccard Drive  
Rockville, MD 20850

FEB 20 1991

William L. Hunt, Ph.D.  
Director, Regulatory Affairs  
Family Health International  
P.O. Box 13950  
Research Triangle Park, North Carolina 27709



Re: G890203/S8  
REALITY™ - Intravaginal Pouch  
Dated: January 16, 1991  
Received: January 23, 1991

Dear Dr. Hunt:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing to change the investigational labeling for the REALITY™ device. Your supplement is approved, and you may implement that change at the institutions previously enrolled in your investigation.

If you have any questions, please contact Raju G. Kammale, D.V.M., Ph.D. at (301) 427-1180 to Nancy F. Teague at (301) 427-1190.

Sincerely yours,

Lillian Yin, Ph.D.  
Director, Division of OB/GYN, ENT,  
and Dental Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health



February 24, 1992

VIA FEDERAL EXPRESS

Dr. Lillian Yin  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

Dear Dr. Yin:

Re: Reality Vaginal Pouch (WPC-333)

Enclosed are three copies of the IDE to perform the Rip/Tear Study as requested by the OB-GYN Devices Advisory Panel at the January 31st review of the Reality PMA.

Dr. Pearlmuter requested we repeat the first study carried out on Reality (1988) but using the 170 mm length devices.

Sincerely,

Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosures

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

signed: 2/26 10:28 M.  
SENDER'S COPY Fud

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Date 2/25/92

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Dr. Mary Ann Leonard

Company

WILLIAM L. CHASE, JR.

Street Address

7-10-11 Colfax Ave ST. 2204

City

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☐ ☐

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(Circuit Court, 1880)

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Food and Drug Administration  
Center for Devices and  
Radiological Health  
1390 Piccard Drive  
Rockville, Maryland 20850

April 1, 1992

WISCONSIN PHARMACAL COMPANY  
919 N. MICHIGAN AVENUE  
SUITE 2208  
CHICAGO, IL 60611  
ATTN: MARY ANN LEEPER

Dear Sponsor:

The information you have submitted, as required by the Food and Drug Administration (FDA) investigational device exemptions (IDE) regulation, has been assigned the following document control number:

IDE Number: G920064

Dated: 03/31/92

Received: 04/01/92

Device: REALITY- INTRAVAGINAL POUCH RIP TEAR STUDY

FDA will notify you when the review of this submission has been completed or if any additional information is required. In accordance with Section 812.30 of the IDE regulation, you may begin your investigation 30 days after the date FDA received your submission, unless FDA notifies you that your investigation may not begin.

Any administrative questions concerning this submission should be directed to the IDE staff at (301) 427-1190. Any future correspondence regarding this submission should be identified with your IDE number and should be submitted, in triplicate, to:

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Document Mail Center (HFZ-401)  
1390 Piccard Drive  
Rockville, Maryland 20850

Sincerely,

*Deborah Falls*  
Michael J. Blackwell, D.V.M., M.P.H.  
Chief, IDE Section  
Program Operations Staff  
Office of Device Evaluation  
Center for Devices and  
Radiological Health



# Wisconsin Pharmacal Company

ACTIVITY ♦ INNOVATION

4/13/92

March 31, 1992

VIA FAX AND FEDERAL EXPRESS

Mr. Colin Pollard  
c/o IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food & Drug Administration  
1390 Piccard  
Rockville, Maryland 20850

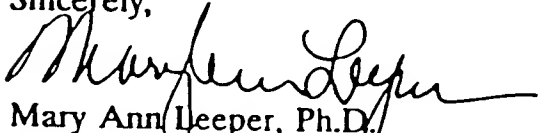
Dear Colin:

Re: Reality Vaginal Pouch (WPC-333)

Since you were not available, I related to your secretary that another three copies of the IDE for the Rip/Tear Study would be forwarded to you. They are enclosed. I have also attached previous communications to you which show that FDA did receive this same IDE on February 25, by M. Courtney, at 10:16 in the morning.

Since FDA has had the IDE for over 30 days, I'm sure that you will see that the review is completed as quickly as possible so we can get the study started. While the 30-day time limit has expired, we choose to wait for FDA's input and hope that it will be received very soon.

Sincerely,



Mary Ann Deeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosures

CC: Dr. Lillian Yin

My Location: Wisconsin Pharmacal Company  
919 N. Michigan Avenue, Suite 2208  
Chicago, Illinois 60611  
Telephone: (312) 280-8541  
Fax: (312) 280-9360

**SENDER'S COPY**  
**OFF YOUR PACKAGE AND SAVE**

It is the IDE

[illegible]

**Wisconsin  
Pharmaceutical  
Company**

CITY ♦ INNOVATION

April 30, 1992

VIA FEDERAL EXPRESS

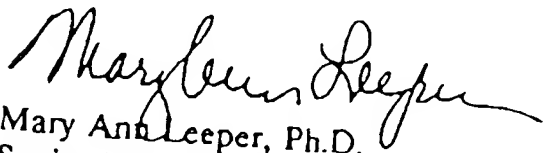
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Re: G920064  
Reality Vaginal Pouch (WPC-333)  
Dated: February 14, 1992  
Received: April 1, 1992

Enclosed are three copies of the responses to FDA's questions to the Reality Vaginal Pouch IDE #G920064.

This is submitted to FDA prior to start-up of the study (May 12) and within the 45 day time allotment.

Sincerely,



Mary Ann Leeper, Ph.D.  
Senior Vice President of Development

MAL/dlp

Enclosures

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## PRELIMINARY REPORT

### A female condom (Femshield™): a study of its user-acceptability

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#### Summary

Twenty-four self-selected married or cohabiting patients age 21 to 56 years evaluated the Femshield during 147 acts of coitus. Fifty per cent of the women and 54 per cent of the men considered the Femshield an acceptable method, and the vast majority of couples (87 per cent) perceived the device to be an effective contraceptive. Moreover, 63 per cent of the men and 79 per cent of the women reported that, in comparison to the male condom, the effect on sexual pleasure was either no different or better. However, analysis of detailed assessments after each use has suggested some improvements to its present design. It is hoped that, with appropriate modifications, the user acceptability of this novel device can be improved, and thus lead to a useful method in the prevention of unwanted pregnancy and sexually transmitted diseases (STDs).

#### Introduction

Male condoms have been used for many years as contraceptives and to prevent the spread of STDs. Their acceptance by the public is limited by perceived and real drawbacks of the method, including lack of sexual spontaneity, reduced sensitivity for the male, aesthetic objections, and reservations about efficacy. Moreover, the method requires a high degree of user motivation, and cooperation by the male

partner. However, with the advent of AIDS (acquired immunodeficiency syndrome), only a mutually faithful monogamous relationship or the use of condoms can be expected to limit the spread. This makes it desirable to develop variants that are free from the above listed drawbacks. With this aim in mind, researchers have begun to develop entirely new types of condoms for use by the female, and in 1987 the Margaret Pyke Centre (MPC) was invited to evaluate the user acceptability of a novel device, soon to be marketed under the name 'Femshield'. This report describes the experience of 24 couples who tested the Femshield during 147 acts of sexual intercourse.

#### Materials and methods

The Femshield was developed by an international multidisciplinary team and is manufactured by the UK company Medicor International PLC. Combining features of a male condom and a diaphragm, the version tested consists of a soft, loose-fitting thermoplastic polyether polyurethane sheath 15cm in length, the open end of which is attached to a 70mm diameter flexible polyurethane ring. A separate, removable polyurethane ring, 65mm in diameter, lies inside the condom where it serves as an introducer and as a means of anchoring the device in the vagina (see figure). Once inserted,

Figure Femshield female condom



the outer ring lies against the vulva and protects it and the base of the penis during intercourse. Its potential advantages, compared to a male condom, include the following:

- Its use is under the woman's control.
- It may be inserted well in advance of intercourse.
- Because of its loose fit, it may cause less loss of sensitivity and permit penetration before complete erection of the penis.
- It may afford greater protection against STDs.
- It is said to be stronger than latex condoms and hence less likely to rupture.
- It permits continued intimacy in the resolution phase after intercourse.

Depending on user preference, the Femshield may be inserted:

- a) manually by the female by compressing the inner ring and sliding the device into the vagina as when inserting a diaphragm (though the inner ring need not be

positioned over the cervix);

- b) manually by the male, as above;
- c) without the inner ring over the erect penis, like a male condom.

Volunteers were self-selected from among the MPC clinic clientele and the general public. Twenty-four married or cohabiting women age 21 to 56 years (mean 31 years) and their partners were recruited. (A further four couples who joined are excluded from this report because they are known not to have started the trial for entirely personal reasons.) All were protected against pregnancy throughout the study by means of hormonal methods (79 per cent) or because they had been sterilised (21 per cent). All patients had past experience of the use of male condoms (20 with their present partner), which 14 (58 per cent) regarded as an acceptable method. Detailed medical, gynaecological and contraceptive histories were recorded. Initial pelvic examination and laboratory tests were performed, including cervical smear, chlamydia screening, and high vaginal swab cultures.

Participants were then invited to try out up to 10 Femshields each and to document their experience after each use on detailed structured questionnaires, to be completed separately by each partner. On conclusion of the study, couples were required to complete a questionnaire jointly, recording their overall experience with the method. Verbal and written instructions on the correct use of the Femshield were provided, with the option of adopting any of the above described insertion techniques, as desired. Patients were permitted to remove the inner ring after inserting the device, if preferred. As the Femshield model used in this study was non-lubricated, patients were given a separate lubricant (KY Jelly) with instructions to apply it to both sides of the condom.

### Results

One hundred and forty-seven Femshields were used by the 24 couples, ranging from one to 12 per couple (mean = 6). Their overall assessment of the method is listed in Table 1. Though approximately 50 per cent of users considered the Femshield an acceptable method, individual perceptions varied widely (as applies to all methods of contraception), ranging from great enthusiasm for, to downright rejection of the method. Analysis of 147 coital acts involving the use of the Femshield revealed that:

Table 1 Overall assessment (N = 24)

		F		M	
		No	(%)	No	(%)
Written instructions on use:	Clear	21	(87)	20	(83)
	Unclear	3	(13)	3	(13)
	NR	0	(0)	1	(4)
Did you find Femshield easy to use	Yes	16	(67)	20	(83)
	No	8	(33)	4	(17)
Did you find Femshield acceptable:	Yes	12	(50)	13	(54)
	No	10	(42)	11	(46)
	Undecided	2	(8)	0	(0)
Effect on sexual pleasure compared to a male condom:	No difference or better	19	(79)	13	(63)
	Worse	5	(21)	9	(37)
Would you prefer Femshield to a male condom:	Yes	12	(50)	9	(37)
	No	11	(46)	12	(50)
	NR/ambiguous	1	(4)	3	(13)
Would you prefer Femshield to a diaphragm: <sup>a</sup>	Yes	8	(53)		
	No	6	(40)		
	Ambiguous	1	(7)		
<sup>a</sup> (Reply based on 15 ex-diaphragm users)					
Would you recommend it to friends:	Yes		12	(50)	
	No		11	(46)	
	Ambiguous		1	(4)	
Do you consider teaching by doctor/nurse needed	Yes		4	(17)	
	No		20	(83)	
Likely to give good contraceptive protection:	Yes		21	(87)	
	No		3	(13)	

NR = not recorded. F = female. M = male

the method was most frequently inserted manually by the female (57 per cent of the time); only 12 per cent of insertions were considered difficult.

and, though insertion well in advance of sexual intercourse was permitted, the majority of cases (77 per cent) involved insertion 10 minutes prior to coitus.

Details of assessment by the female are listed in Table 2.

As can be seen, the Femshield did not cause any discomfort to the female in the majority of coital acts (72 per cent) and, though the outer ring was felt by the women in 39 per cent of instances, this was generally considered to be acceptable. However, the finding of a reduction

in sexual pleasure, for example during foreplay, in 47 per cent of coital acts may adversely affect women's acceptance of this new method. Condom breakage during intercourse, as documented in three per cent of cases (Table 2) may be related to the presence of a seam in the version tested.

Details of assessment by the male are listed in Table 3. Although, in the overall assessment, more than half of all males stated that they found the method acceptable, analysis of their detailed replies reveals various reservations. In 62 per cent of coital acts involving the use of the inner ring, the males stated that they could feel it. A preference for the Femshield to be pre-lubricated, seamless and longer was also expressed by many.

Table 2 Assessment by the female (N = 147 coital acts\*)

		N	(%)
Did you feel the outer ring:	No	90/147	(61)
	Yes	57/147	(39)
Did you feel the inner ring, when used:	No	57/89	(64)
	Yes	32/89	(36)
Did the Femshield tear during insertion:	No	147/147	(100)
	Yes	0/147	(0)
Did the Femshield tear during intercourse:	No	142/147	(97)
	Yes	5/147	(3)
Did penis enter 'the wrong place' (behind/in front of the Femshield):	No	141/147	(96)
	Yes	6/147	(4)
Did Femshield reduce your sexual pleasure (eg during foreplay):	No	78/147	(53)
	Yes	69/147	(47)
Orgasm in comparison with your usual experience:	Better	13/142	(9)
	As usual	88/142	(62)
	Reduced	41/142	(29)
Did Femshield cause you any discomfort:	No	105/145	(72)
	Yes	40/145	(28)

\*Numerator differs for some questions because patient's reply ambiguous or not always recorded

Table 3 Assessment by the male (N = 147 coital acts\*)

		N	(%)
Do you like the Femshield:	No	58/134	(43)
	Yes	76/134	(57)
Can you feel the inner ring, when used: (ring was not used in 51/146 instances)	No	36/95	(38)
	Yes	59/95	(62)
Does the Femshield reduce your sexual pleasure:	No	49/146	(34)
	Yes	97/146	(66)
Orgasm in comparison with your usual experience:	Better	20/143	(14)
	As usual	72/143	(50)
	Reduced	51/143	(36)
Does the Femshield cause you any discomfort:	No	116/146	(79)
	Yes	30/146	(21)

\*Numerator varies because patient's reply to specific questions ambiguous or not always recorded

### Discussion

There is undoubtedly a need for new and better barrier methods which, apart from providing effective contraception, protect against STDs, particularly AIDS. The invention of the Femshield has raised much hope among the public and family planning researchers and providers, including the World Health

Organisation, that this type of condom could fill this unmet need. No firm conclusions can be drawn from this very preliminary assessment because the number of patients involved was very small and they were not a representative sample, as all were self-selected and had previously elected to use a non-barrier contraceptive. Nevertheless, the study has made a valuable

Contribution to the development of the Femshield by identifying aspects of the present design which require modification. In particular our patients' clear preference (in their open-ended remarks) for a pre-lubricated, seamless and longer condom needs to be addressed, as do their reservations about the inner ring. Steps are now being taken by the manufacturer to refine the Femshield, incorporating some of our recommendations. Further clinical and laboratory studies are already in progress or planned in Scandinavia, Germany, the UK and in the USA, involving clinical trials to determine use-effectiveness; and in vitro studies to assess the non-permeability of the Femshield membrane by viruses, including the Human Immunodeficiency Virus (HIV). Already, Conant et al have demonstrated that the cytomegalovirus and the human immunodeficiency virus do not permeate the Femshield membrane. The study, to be published in JAMA, involved simulated coitus in a virus-containing inner Femshield suspended in

a tissue culture-containing outer Femshield (Conant et al. Personal Communication via Dr Paul Salmon of Medicor, August 1988).

Clinical and microbiological studies to determine the Femshield's protective potential against STDs are also planned in collaboration with the World Health Organisation.

The concept of a female condom has attracted much public interest. Although the majority (87 per cent) of our study participants felt that the Femshield would be an effective contraceptive, certain open-ended comments we received as well as some of the replies in Tables 1-3, imply that the tested version leaves room for improvement. With appropriate modifications in its structural design and method of use, the Femshield may come to play an important role in the prevention of unwanted pregnancy and the spread of sexually transmitted diseases.

**Acknowledgements**

We thank Medicor International PLC for financial assistance and free supplies of the Femshield, the study participants for their cooperation, and Gillian Corne for clerical help with this project.



QUALITY ♦ INNOVATION

April 20, 1993

Chartex International Plc  
33 Cavendish Square,  
London W1M 9HF

Attention: President

Dear Sirs

The Wisconsin Pharmacal Company, Inc., is the holder of the regulatory approval granted with respect to the regulatory review period for the medical device known by either the mark REALITY or the mark FEMIDOM. The device is a vaginal pouch and is described and claimed in three patents assigned to Chartex International Plc which are U.S. Patent Numbers 4,735,621, 4,976,273, and 5,094,250. Chartex International Plc holds express and exclusive authorization from the Wisconsin Pharmacal Company, Inc., to rely upon the regulatory review period as the basis for the application for extension of the term of any one of the Chartex International Plc patents for the device.

Very truly yours,  
WISCONSIN PHARMACAL COMPANY, INC.,

By

Name: John Wundrock  
Title: President

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